SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF ANALOGUES OF NICOTINE

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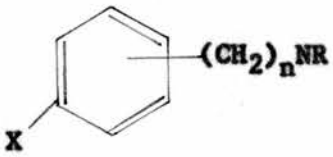
CONTENTS

ABSTRACT

This thesis describes the preparation of analogues of nicotine, having the following structure:-



where NR = NEt_2, $\overset{+}{N}Et_3$, $\overset{+}{N}Me_3$;

n = 1, 2 and 3;

X = NO_2, Cl, Br, OMe, OH and NH_2

These have been tested on the frog rectus abdominis preparation, which contains receptors sensitive to nicotine.

Most of the trimethylammonium compounds acted like nicotine and their relative activities have been measured. Most of the other compounds blocked the receptors and their affinity constants have been measured. The pK_a values of the tertiary bases have also been determined.

An attempt has been made to correlate the effects of changes in chemical structure on the affinity of the blocking agents, with the electron-releasing or electron-withdrawing effects of the substituent, X, as shown by its effect on the pK_a of the tertiary bases. No obvious relationship was noted, nor was there any obvious connexion between the affinity and the size of the substituent, X, or the number of methylene groups, n, in the chain. By far the most active blocking agent was p-hydroxybenzyldiethylamine, but in general the most active compounds were the chloro-substituted derivatives.

The nature of the substituent, X, and the length of the chain, n, had profound effects on the ability of compounds to stimulate the preparation. The most active, m-hydroxyphenylpropyltrimethylammonium, was about 5 times

as active as the standard, β-pyridylmethyltrimethylammonium, i.e., about 40 times as active as nicotine. The next most active compounds were p-, m-, and o-aminophenethyltrimethylammonium, which were 2.5, 0.55 and 0.28 times as active as the standard. In general the most active compounds contained groups which were not particularly associated with high affinity in the antagonists. This suggests that they were active, not because they were strongly bound to the receptors, but because they were particularly well able to activate them. Usually the o-compounds were only feebly active, but as the corresponding antagonists had reasonable affinity, it seems that the o-substituent markedly reduces the ability of the compound to activate the receptor. The number of methylene groups (n) in the chain was important for activity; usually the most active compounds had two methylene groups, with the notable exception of the most active compound of all, m-hydroxyphenylpropyltrimethylammonium. The benzyl derivatives were much weaker.

Although it has not been possible to correlate satisfactorily the biological activity with the size and nature of the substituent and the length of the chain, there is still reason to believe that these are extremely important. The chemical properties of the compounds should be studied further and, in particular, an attempt should be made to find the most favoured conformations in solution, using nuclear magnetic resonance spectroscopy.

INTRODUCTION

Introduction

The physiological activity of nicotine at ganglia was noted by Langley and Dickinson (1889). Application of a solution of nicotine to the superior cervical ganglion of a cat caused dilatation of the pupil, the same effect as was produced by electrical stimulation of the sympathetic nerve trunk. At parts of the nerve other than the ganglion, nicotine did not produce this effect. Subsequent electrical stimulation of the preganglionic nerve caused no dilation of the pupil. Langley concluded that nicotine stimulated and then blocked the ganglion.

Using nicotine as a tool, Langley was able to show the location of the ganglia in the cat. Nicotine was applied to the nerve, and if stimulation followed by block occurred, a ganglionic synapse was supposed to be present.

A study of various esters and ethers of choline was made by Dale (1914). He divided the actions of acetyl choline into two categories: "nicotinic and muscarinic". The alkaloid muscarine was active at the postganglionic parasympathetic site, and nicotine was active at ganglia. The effects of muscarine were unaffected by large doses of nicotine but readily abolished by atropine, and the stimulant effect of nicotine was abolished by excess of nicotine.

At the neuromuscular junction, nicotine, like acetylcholine, produces a slow, long-lasting contraction on certain muscles of the frog and the chick (for example, frog rectus muscle). This is called a contracture to distinguish it from the twitch response which nicotine and acetylcholine produce when applied to other types of skeletal muscle (for example, frog sartorius muscle). In larger doses the stimulant activity is followed by a block in transmission. The block in transmission has been shown by microphysiological techniques

(Thesleff 1958) to be caused by desensitisation of the receptors rather than by reversible competition.

Compared with acetylcholine, the effects of nicotine at the neuromuscular junction are smaller than its effects at ganglia. As a ganglion stimulant, nicotine has about the same activity as acetyl choline in the presence of eserine (Feldberg & Vartiainen 1934), although in the absence of eserine acetylcholine is less active. At the neuromuscular junction nicotine has about one hundredth the activity of acetylcholine (Bacq and Brown 1937). Thus, at both the ganglion and the neuromuscular junction, nicotine produces similar effects to acetylcholine, that is, stimulation followed by block. The block produced by nicotine is, however, of a greater duration than that produced by acetylcholine, especially at the neuromuscular junction.

Structure-Activity Relationships

One of the first attempts to correlate chemical structure with nicotine-like activity was made by Hey (1952) who also reviewed previous work. He suggested that nicotine-like stimulant activity was associated with the following structure:

$$\overset{\delta+}{RO} - (CH_2)_2 \overset{+}{N}Me_3$$

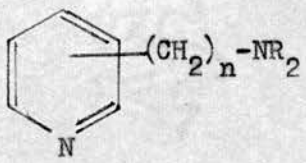
and that the most active compounds would occur when $\delta+$ was large.

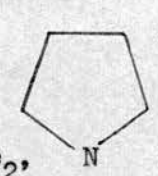
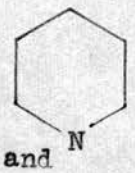
To test this hypothesis, Hey tested substituted phenyl ethers of choline on the blood pressure of the atropine pretreated cat. Substituents in the benzene ring included m - and p - chloro, m - and p - methyl, m-bromo, 3, 5-dibromo, and 3, 5-dimethyl. The groups chosen had similar van der Waals diameters, which made it unlikely that activity differences were due to variation in ion size. Meta substituted halogen groups are mainly electron withdrawing due to the inductive effect, but methyl groups would increase electron density in the benzene ring. These groups would thus increase and decrease respectively the δ + on the ether oxygen. Hey found the halogen substituted compounds to be more active than phenyl choline ether, which was, in turn, more active than the methyl substituted compounds. The p-chloro compound was rather more complicated; as well as the -I effect there is a mesomeric effect tending to decrease the δ + on the ether oxygen. This compound was more active than phenyl choline ether but less active than the m-chloro substituted analogue. These results fitted his hypotheses.

However, in the benzoyl esters of choline, tested on the cat ganglion by Ormerod (1956), the substituents had the reverse effect. Also, the differenes

in activity of the esters were smaller than for the ethers. In the esters, an electron-withdrawing substituent would increase the polarisation of the carbonyl group. Because of the strong polarisation of the carbonyl group it is unlikely that the ether oxygen would acquire a positive charge. This would also explain the low activity of the esters compared with the ethers.

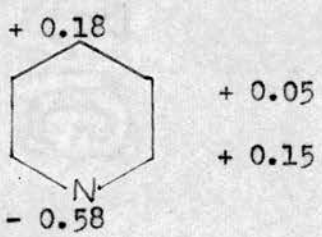
As an extension of Hey's theory, Barlow and Hamilton (1962) studied pyridine analogues of nicotine, with the following general formula:



n = 1 and 2; NR_2 = NMe_2,  and 

and some quaternary salts derived from them.

The π electron charge distribution of the pyridine ring has been calculated by the molecular orbital method of Longuet-Higgins and Coulson (1947). The relative charges are



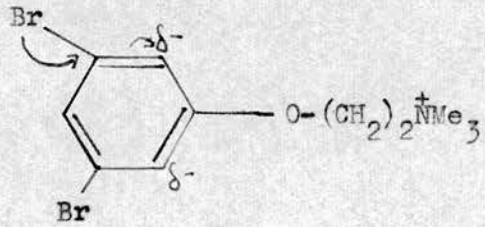
Therefore to give support to Hey's theory, the β -pyridyl member of the series should always be the most active. On the cat superior cervical ganglion and the chick biventer, this was almost always the case. The only exception was that β- and γ-pyridylmethyltrimethylammonium compounds were equiactive on the chick biventer. On the rat diaphragm, however, the β- compound was not always the most active. Hamilton and Rubinstein (1968) have studied some of these compounds on the frog rectus and found the β - compound to be the most active.

An alternative theory to Hey's has been put forward to explain nicotine-like activity. As a result of studying senecioylcholine, which shows marked pressor action and negligeable muscarinic activity, Sekul and Holland (1961a) suggested that nicotine-like activity results from increased electron density at the carbonyl oxygen, and muscarinic activity is caused by diminished electron density at the ether oxygen. In this ester, the double bond system favours a δ - on the carbonyl oxygen by the following interaction.

$$(CH_3)_2C = CH-\overset{\overset{O}{\|}}{C}-OCH_2 - CH_2 \overset{+}{N}Me_3 \qquad (CH_3)_2\overset{+}{C} - CH = \overset{\overset{O^-}{|}}{C}-OCH_2CH_2 \overset{+}{N}Me_3$$

This also reduces the electropositivity of the ether oxygen, since the charged carbonyl oxygen cannot exhibit an electron withdrawing effect.

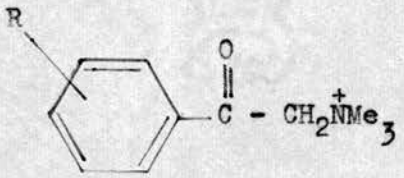
To further test this theory, Sekul and Holland (1961b) tested a number of unsaturated esters of choline which had the double bond in the same place as in senecioyl choline, and their saturated analogues. The unsaturated compounds did not exhibit muscarinic activity, but showed increased nicotine-like behaviour compared with the corresponding saturated compounds. Furthermore, methyl substitution in either the α or β position of the unsaturated analogues enhanced activity. They suggested that this could be due to the inductive effect of the methyl group. Sekul and Holland also explained the high activity of Hey's 3, 5-dibromo compound in terms of the mesomeric effect of the substituent bromines.



This results in δ - charges on the atoms shown. These are in analagous positions to the carbonyl oxygen in acetylcholine.

Coleman, Hume, and Holland (1965) tested some meta substituted phenylcholine ethers on the blood pressure of the dog and the cat, and on the cat superior cervical ganglion. The substituents studied were NO_2, F, Cl, Br, I, NH_2. The inductive effect of these groups is in this order, nitro being most electron withdrawing, and amino least. Because the meta position was chosen, the mesomeric, electron releasing effect of the halogens and the amino group could be ignored. The fact that the reverse order of nicotinic activity was noted does not agree with Hey's hypothesis. Coleman et.al. suggested the polarisability of the system, rather that a permanent polarisation might be important, since it would relate to the moment of interaction of the ether with the receptor. The estimated polarisability of the substituents agreed with the nicotine-like stimulant action of the ether.

A similar study of keto derivatives was made by Wong & Long (1962) who tested the following compounds on the blood pressure of atropinised dogs.



R = 4.Cl, 4-Br, 4-NO_2
2,4-diCH_3, 4-NH_2

They found a qualitative agreement between the sigma values of the para substituents, calculated from the Hammett equation, and their nicotine-like activity. The amino substituted compound was most active and the nitro compound least active. Recently, Kier (1968) has worked out interatomic distances and charge distributions for preferred conformations of the nicotinium ion and acetylcholine using the extended Hückel theory. He suggests

the existence of two "rotamers" of nicotinium with identical energies, formed by turning the pyrrolidine ring through 120° and 300° with respect to the pyridine ring. Kier compared the interatomic distances of these rotamers with acetyl choline, and found that, in the 120° rotamer, a correlation exists. The pyridine nitrogen atom has a substantial negative charge and is 4.76 Å from the quaternary nitrogen atom. In acetylcholine, the negatively charged oxygen atom is 4.93Å from the quaternary nitrogen when the acyl group is in a 120° orientation to the ether oxygen-carbon bond. This is a permitted conformation of acetylcholine.

From these observations, Kier concludes that the criterion for nicotinic behaviour is a $\delta-$ charge, 4.85 ± 0.1Å from the quaternary nitrogen atom. However, Gill (1965) has pointed out that, depending on the energies involved in altering the conformation of the molecule, and the energy of the drug-receptor interaction, the preferred conformation may not be the one contributing to its activity. With this in mind, it would be interesting to calculate conformations of the most active nicotine-like compounds.

Barlow and McLeod (1968 in press) have studied the alkaloid cytisine which has a fairly rigid structure. Models show that the nitrogen atom in ring C of cytisine appears to be about 4.85 Å from the partially negatively charged oxygen atom of the pyridone group. However, this correlation also exists in the quaternary derivative of cytisine, which possesses no nicotine-like activity.

All these theories have involved the comparison of agonist drugs. The activity of such a drug depends on two factors: its affinity and its efficacy. Because changes in the molecule may affect either of these properties in

different ways, Barlow, Scott and Stephenson (1963) studied series of agonists, and their corresponding antagonists, on the muscarine sensitive receptors in the guinea pig ileum. The affinity constants for antagonists and partial agonists were measured (see practical section). The variation of the affinity constant with the composition of the onium group in the antagonists was sufficiently consistent from one series to another for it to seem likely that corresponding changes in affinity with the constitution of the onium group would occur in the agonists. From the relative activity of the agonists, and with the knowledge of relative affinity, they were able to assess the effects of structure on efficacy.

This approach has been criticised by Burgen (1965), who studied the carbon analogue of acetylcholine, 3,3-dimethylbutyl acetate. This produced similar responses to acetylcholine and has an equipotent molar ratio of 3,170. Using the method of Nickerson (1956), Burgen estimated the receptor reserve for acetylcholine on the guinea pig ileum, using dibenamine as an irreversible blocking agent, and found it to be very low. He argued that the low activity of 3,3-dimethylbutyl acetate was due to a reduction in affinity rather than reduced efficacy. Calculations, based on the difference in free energy of interaction of acetylcholine and dimethylbutyl acetate showed that the equilibrium distance of the quaternary nitrogen atom from a negatively charged group in the receptor was 3.29 $\mathring{A}$, close to that measured on models. For benziloyl choline the distance was 4.96 $\mathring{A}$. Burgen suggested that the ability of a compound to act as an agonist depends on it achieving the equilibrium distance, and that, in benziloyl choline, the large bulk of the molecule displaces the cationic head from the equilibrium distance. This results in benziloyl choline being an antagonist.

From results obtained by comparing the affinity constants of diphenylacetoxyethyl and benziloyl compounds with different onium groups, Scott (1967) has suggested that it may be valid to estimate the affinity of series of agonists by studying corresponding series of antagonists so long as the change in the onium group involves only replacement of methyl by ethyl. When other groups were introduced (methyl and ethyl pyrrolidine and piperidine) the effects of the replacement in the two series were not the same.

It would seem likely that, although a large change such as replacement of acetyl by benziloyl, might produce a change in relative affinity of the molecules, small changes would not influence the relative affinity very much.

Related Compounds

Some of the compounds to be examined have already been tested, although not always quantitatively.

Barger and Dale (1910) described p- hydroxyphenethyltrimethylammonium (hordenine methiodide) as being "very active".

Ing and Wright (1934) found that phenyl, benzyl, and β -phenethyltrimethylammonium caused contracture of the frog rectus. They did not compare the activities. Phenyltrimethylammonium was found to have only nicotinic activity by Wong and Long (1962). Benzyltrimethylammonium had only muscarinic activity, but phenethyl and phenylpropyltrimethylammonium had increasing nicotinic behaviour. Scott (1967) has studied the series of compounds.

$$Ph\ (CH_2)_n\ \overset{+}{N}Me_3 \qquad \text{where } n = 0 \text{ to } 5$$

and found that the phenylpropyl compound was most active in producing contracture of the frog rectus preparation.

Erspamer and Glässer (1960) extracted the substance leptodactyline (m-hydroxyphenethyltrimethylammonium) from the skin of lizards and found that it had marked nicotine-like behaviour (equipotent molar ratio relative to acetylcholine of 0.11 to 0.14 on the frog rectus). A number of analogues of leptodactyline were studied by Glässer and Pasini (1960). They tested substituted phenethyltrimethylammonium salts and found the following order of activity on the frog rectus:

3-OH > 3,4-dihydroxy > 3-Cl > 4-OH > 3-Methyl > 3,4-dimethoxy > 2-hydroxy.

leptodactyline, which was the most active compound studied, bears a strong

structural resemblance to β -pyridylmethyltrimethylammonium.

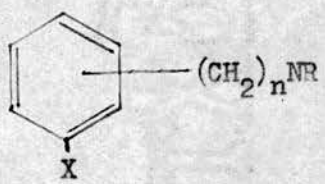
Bromo substituted benzyltrimethylammonium salts were tested by Credner (1958) who reported that the para compound exhibited considerable nicotinic behaviour, but the ortho and meta isomers had only musarinic action.

Methyl substitution of benzyltrimethylammonium was found to reduce the activity of the unsubstituted compound. (Levy, Mathieu, and Michel-Ber, 1958). The para compound exhibited the greatest nicotine-like stimulating activity but the ortho compound was without activity.

None of these studies give any idea of the relative effects of substituents in the benzene ring because in each case, only a small number of compounds were tested under comparable conditions.

Aim of Work

It was intended to study the effects of chain length and ring substituent on the affinity and efficacy of compounds having the following general formula.



$NR = \overset{+}{N}Me_3$, NEt_2, $\overset{+}{N}Et_3$

$X = NO_2$, Cl, Br, OMe, OH, NH_2

n = 1, 2, and 3.

They were all tested on the frog rectus preparation for stimulant and blocking activity. The diethylamine and triethylammonium compounds should be antagonists, and it should therefore be possible to study the effects of chemical structure on affinity. If this information can be transferred to the trimethylammonium compounds, which are mostly agonists, it should be possible to deduce the effects of chemical structure on efficacy.

The effect of the substituent on the charge of the onium group can be assessed by comparing the ionisation constants of the corresponding tertiary bases, and an attempt has been made to see if this is related to the biological properties of the compounds.

EXPERIMENTAL

Frog Rectus Abdominis Preparation

A frog (Rana Pipiens) was killed and the skin of the abdomen opened. The base of the sternum was cut through and the two rectus muscles dissected out. When very large frogs were used, each rectus muscle could be split longitudinally, giving four strips in all. More usually each muscle was used for one preparation. Each end of the strip was tied with thread and suspended in an organ bath containing Clark's ringer solution. This had the following composition.

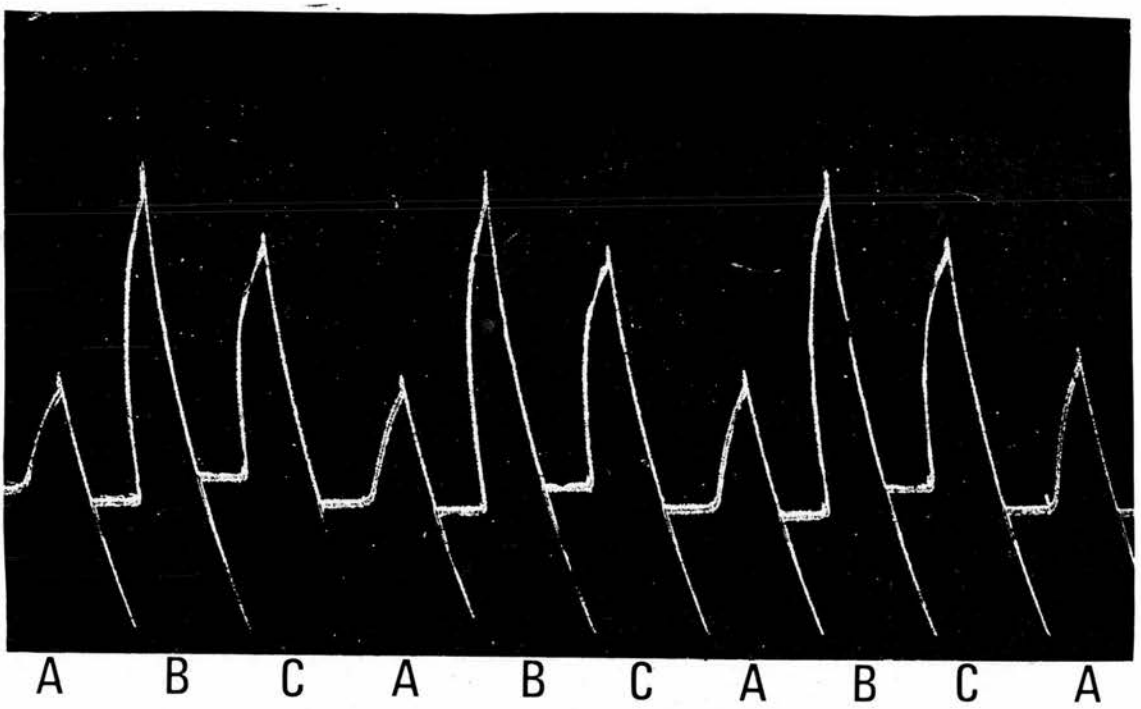
Na Cl	6.5 g/l
K Cl	0.14 g/l
$CaCl_2$	0.12 g/l
NaH_2PO_4	0.01 g/l
$NaH\ CO_3$	0.4 g/l

The preparation was gassed using an aerator, and contractions of the muscle were recorded using an isotonic gimbal-mounted lever which wrote on the smoked paper of a kymograph. The load on the muscle was about 0.5 g.

All drugs, in the required concentrations, were contained in reservoirs above the bath. The solutions flowed onto the tissue at the appropriate time by opening a magnetic relay, which was operated by a time clock and a uniselector. The agonist was in contact with the tissue for $4\frac{1}{2}$ minutes. The tissue was then washed, and a 5g. load gently applied for 15 minutes to stretch the muscle. During this time the tissue was washed twice more. The second dose of drug was added 30 minutes after the first. The long time

FIGURE 1

Bracketing assay for agonists.



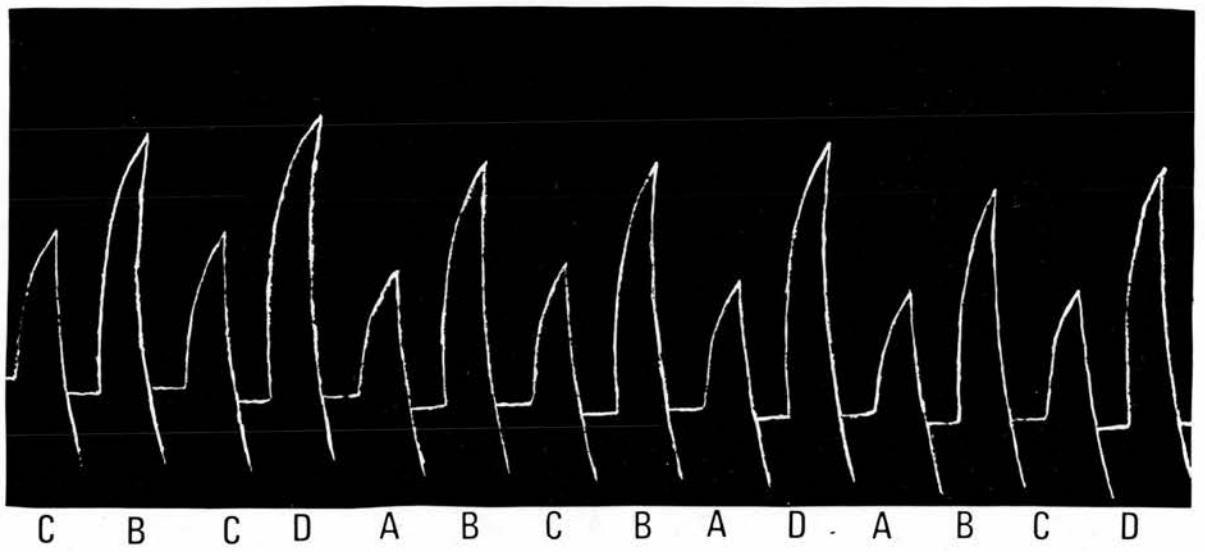
A = 4×10^{-7} β-pyridylmethyltrimethylammonium.

B = 8×10^{-7} β-pyridylmethyltrimethylammonium.

C = 4×10^{-6} m-chlorophenethyltrimethylammonium.

FIGURE 2

2 + 2 assay for agonists.



A = 16×10^{-7} β-pyridylmethyltrimethylammonium

B = 32×10^{-7} β-pyridylmethyltrimethylammonium

C = 4×10^{-5} p-chlorophenethyltrimethylammonium

D = 8×10^{-5} p-chlorophenethyltrimethylammonium.

cycle was necessary because the compounds used were rather slow to wash out. Consistent responses were obtained for at least 24 hours using this method.

Methods (i) Agonists.

Agonist activity was determined by measuring the equipotent molar ratio relative to β-pyridylmethyltrimethylammonium. Two doses of the standard were chosen which gave responses in the middle portion of the logdose-response curve. (Often 8 and 16×10^{-7} molar were suitable). Doses of the unknown were determined which approximately matched the standard responses, and the four solutions were applied in the following order:

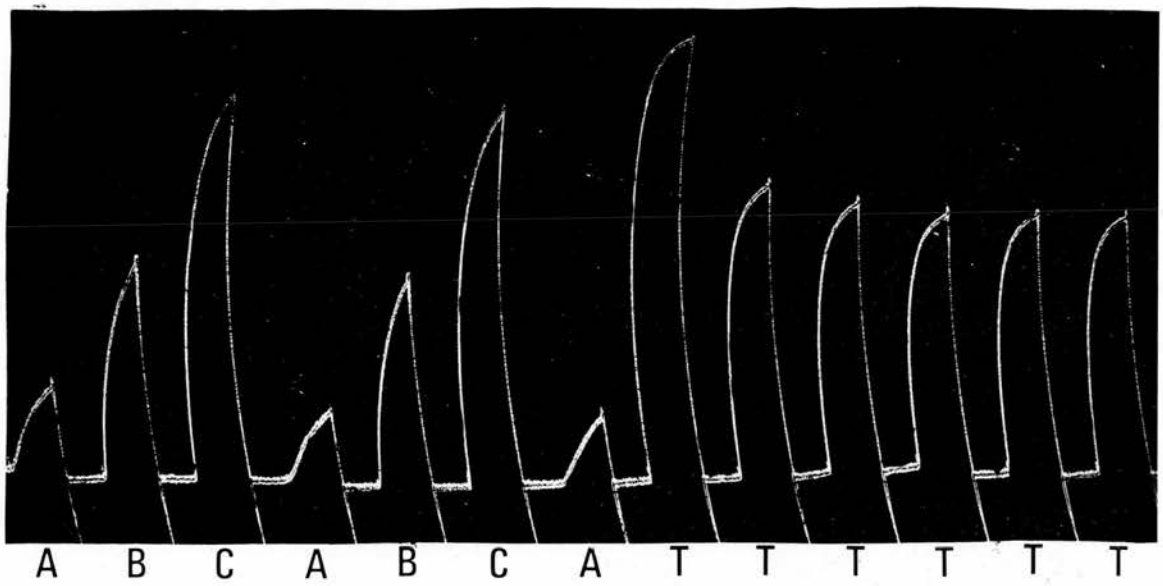
A	B	C	D
A	D	C	B
C	D	A	B
C	B	A	D

where A and C are low doses of standard and unknown respectively, and B and D are high doses of standard and unknown respectively.

Thus 2 + 2 assays could be performed in which a high dose always followed a low dose. This was used to minimise the effect of a large dose on a following large dose. Also bracketing 2 + 1 assays were performed. Figs. 1 and 2 show typical traces for these two methods. The equipotent molar ratio was calculated from the average slope of the logdose-response lines and the average difference in the response size. Each compound was tested on a

FIGURE 3

Measurement of the affinity constant of an antagonist.



A = 4×10^{-7} β-pyridylmethyltrimethylammonium.

B = 8×10^{-7} β-pyridylmethyltrimethylammonium.

C = 16×10^{-7} β-pyridylmethyltrimethylammonium.

T = 10^{-3} m-aminobenzyldiethylamine + 4×10^{-6} β-pyridylmethyltrimethylammonium.

number of preparations. Some compounds gave log dose-response curves not as steep as those for the standard agonist. These were found to be partial agonists.

(ii) Antagonists.

Three doses of standard agonist (usually 4, 8, and 16 x 10^{-7} molar - β-pyridylmethyltrimethylammonium) were applied repeatedly to the preparation. This was continued for several hours (usually overnight) until several consistent responses for each dose were obtained. Ringer and drug solutions were replaced by solutions containing antagonist, and a higher concentration of standard agonist was used, which produced responses lying within the range of the three standard doses. Fig. 3 shows a typical trace. Two to three hours were usually necessary before equilibrium was established. Sometimes the concentrations of antagonist and standard agonist were changed to give another dose ratio.

From the heights of the contractions, the concentration, A, of agonist was found, which, when applied in the presence of concentration B of antagonist, gave the same size of contraction as concentration (a) of agonist did alone.

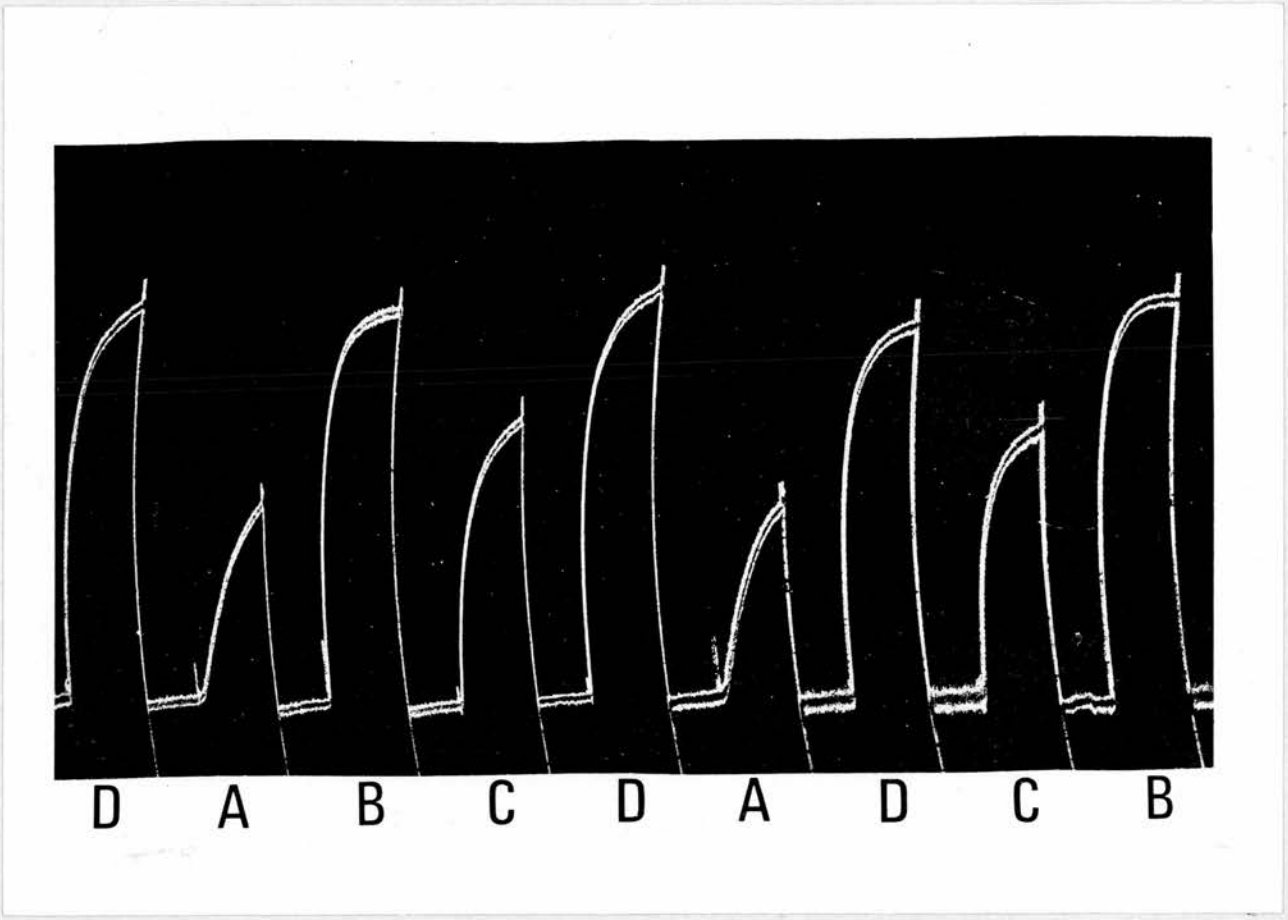
The affinity constant of the antagonist was calculated from the Gaddum equation:

$$BK_B = \frac{A}{a} - 1$$

where $\frac{A}{a}$ is the dose ratio and K_B is the affinity constant. Several determinations of K_B were made for each compound.

FIGURE 4

Measurement of the affinity constant of a partial agonist. (Mixture method).



A = 5×10^{-4} p-aminobenzyldiethylamine

B = 5×10^{-4} p-aminobenzyldiethylamine + 32×10^{-7} β-pyridylmethyltrimethylammonium.

C = 16×10^{-7} β-pyridylmethyltrimethylammonium.

D = 32×10^{-7} β-pyridylmethyltrimethylammonium.

(iii) Partial Agonists.

Compounds which had shallower dose-response lines than that of the standard agonist were also incapable of ellicíting a maximal contraction from the tissue. These were tested by one of two methods. The first was used for compounds which considerably inhibited the response of the tissue to the standard agonist. The second was used for compounds which exhibited considerable agonist activity.

a. Mixture method. (Stephenson 1956)

This method involved finding a concentration A_1, of standard agonist which produced the same contraction as concentration P of partial agonist. Also a concentration A_2 was found, which produced the same response as $P + A_3$ together.

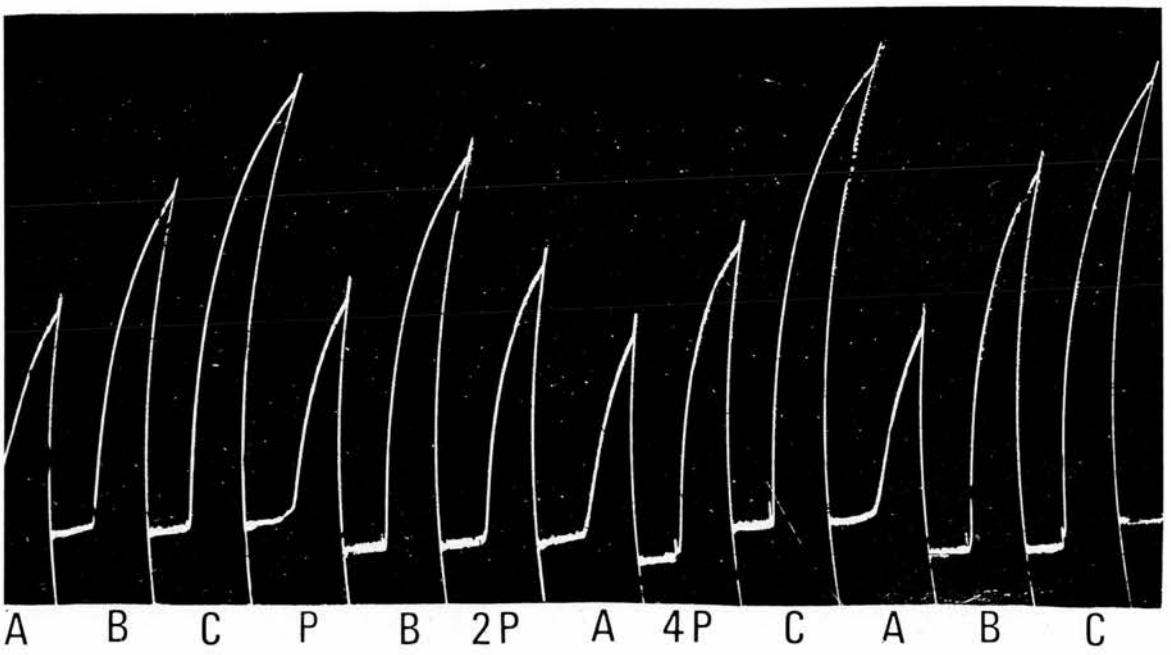
In practice, two concentrations of agonist were chosen, which gave responses in the middle of the dose-response curve. A concentration, P, of partial agonist was found which approximately matched the smaller of the standard contractions, and a concentration A_3 of agonist, which, when applied along with P, matched the larger of the standard contractions. The drugs were applied in the same way as the 2+2 assay for agonists. A_1 and A_2 were found by comparing contractions of the two test solutions with the contractions of the standard agonist. Fig. 4 shows a trace using this method.

Stephenson showed that $$1-x = \frac{A_2 - A_1}{A_3}$$

where x is the fraction of receptors occupied by the partial agonist. Values of Kp, the affinity constant of the partial agonist, can then be

FIGURE 5

Measurement of the affinity constant of a partial agonist. (Reciprocal plot method).



A = 4×10^{-7} β-pyridylmethyltrimethylammonium.

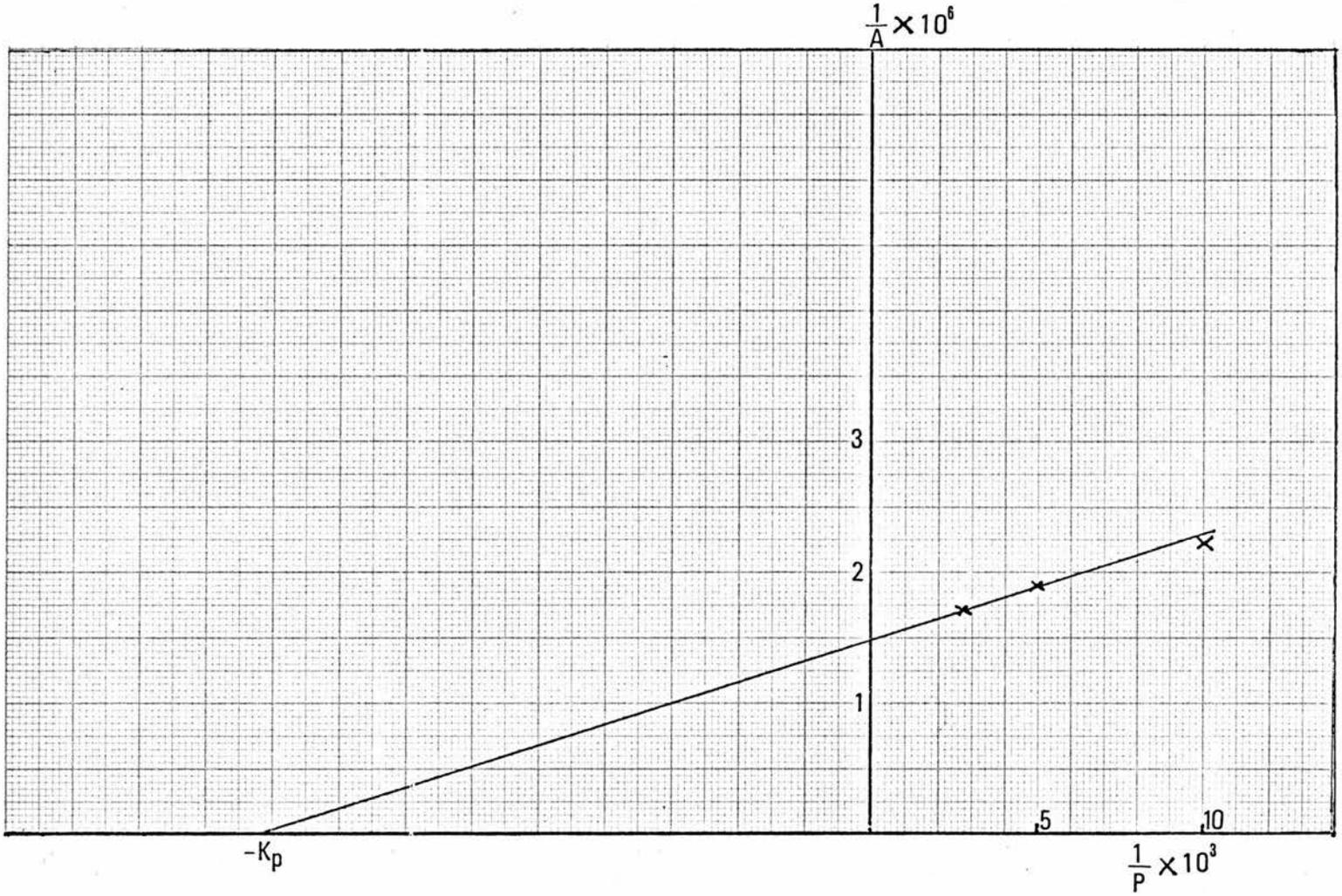
B = 8×10^{-7} β-pyridylmethyltrimethylammonium.

C = 16×10^{-7} β-pyridylmethyltrimethylammonium.

P = 10^{-4} m-chlorophenethyltriethylammonium.

FIGURE 6

Graph of $\frac{1}{A}$ against $\frac{1}{P}$ calculated from the results shown in the tracing.



calculated from

$$Kp.P = \frac{X}{1-X}$$

b. Reciprocal plot method (Barlow, Scott, and Stephenson, 1967).

At least three concentrations of partial agonist were found which gave suitable contractions. By randomly alternating these doses with doses of standard agonist, concentrations of pure agonist could be calculated, which matched each dose of the partial agonist. This is shown in fig. 5. The reciprocals of the partial agonist concentrations ($\frac{1}{p}$) were plotted against the reciprocals of their corresponding agonist concentrations ($\frac{1}{a}$). Fig. 6.

Stephenson has shown that this graph should be a straight line with an intercept, when $\frac{1}{a} = 0$, of $-K_p$.

Determination of Ionisation Constants

The pKa values of some of the tertiary bases were found using the method of Albert and Serjeant (1962).

10^{-4} mole of the hydrobromide or dihydrobromide in ethanol/water (about 40 mls of 40% ethanol) was titrated against standard alkali using a Pye Dynacap pH meter fitted with glass and calomel electrodes. The solution was maintained at 25°C in a water bath and was stirred throughout the titration by blowing a steady stream of nitrogen through the solution. Ethanol was present because of the extreme insolubility of the liberated tertiary base in water. Presence of ethanol produces a depression of the pKa values. The results are the mean of two experiments, which did not differ by more than 0.02 pH unit. Since the compounds are chemically related it is probably valid to compare the values obtained so long as results of great precision are not expected (Albert and Serjeant (1962)).

RESULTS

Table 1 pKa values of XC_6H_4Y.

X	Y	ortho	meta	para
-H	CH_2NMe_2	8.07	8.07	8.07
-Cl	CH_2NMe_2	7.88	7.75	7.94
$-NH_2$	CH_2NMe_2	8.39	8.58	8.94
-H	CH_2NEt_2	8.92	8.92	8.92
$-NO_2$	CH_2NEt_2	8.05	7.96	7.81
-Cl	CH_2NEt_2	8.37	8.29	8.43
-OMe	CH_2NEt_2	9.49	8.58	8.83
$-NH_2$	CH_2NEt_2	8.70	9.12	9.53
-H	$(CH_2)_2NMe_2$	8.63	8.63	8.63
-Cl	$(CH_2)_2NMe_2$	8.33	8.26	not determined
-H	$(CH_2)_2NEt_2$	9.14	9.14	9.14
-Cl	$(CH_2)_2NEt_2$	8.71	8.91	not determined
-Cl	$(CH_2)_3NMe_2$	8.75	8.59	8.79
-Cl	$(CH_2)_3NEt_2$	9.31	9.46	9.50

Results

To present the results in logical sequence, I have arranged the substituent groups in order of electron donating or withdrawing properties. Table 1 shows dissociation constants of some of the tertiary bases. Because the measurements were made in 40% ethanol the pKa values are depressed about one unit from the true value. Thus the true pKa values are in the region of 9 to 10, but comparisons of these results should still give an idea of relative electron withdrawing properties.

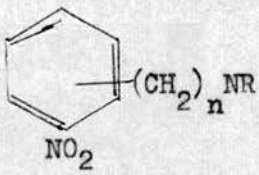
The more strongly electron donating groups have larger pKa values. Thus, in general the electron donating effect appears to be in the order:

$$NO_2 < Cl < Br < OMe < OH < NH_2$$

Pharmacological experiments were performed at pH 7, but at this pH the tertiary bases would be almost totally ionised so that correction of the results to allow for the degree of ionisation is unnecessary.

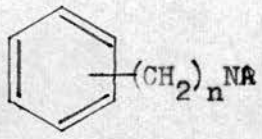
Results of experiments on the frog rectus preparation are shown in tables 2-8. Values which are doubly underlined show the log equipotent molar ratios of agonists relative to β -pyridylmethyltrimethylammonium; values which are singly underlined are log affinity constants of partial agonists; values which are not underlined are log affinity constants of antagonists. The results are the mean of several experiments plus or minus the standard error of the mean, with the number of experiments in parentheses.

Table 8 shows results for the unsubstituted compounds obtained by Scott (1967).

Table 2 Results for 

n = 1	NR	ortho	meta	para
	$^{+}NMe_3$	3.32	1.88	1.67
		±0.04 (6)	±0.05 (5)	±0.02 (5)
	NEt_2	4.41	2.46	2.27
		±0.05 (6)	±0.03 (5)	±0.07 (5)
	$^{+}NEt_3$		4.33	3.11
			±0.04 (7)	±0.14 (6)

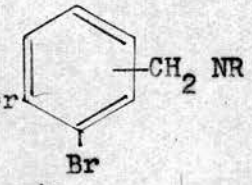
n = 2	NR	ortho	meta	para
	$^{+}NMe_3$	1.71	0.62	1.66
		±0.02 (4)	±0.01 (4)	±0.03 (7)
	$^{+}NEt_3$	4.41	5.30	3.00
		±0.04 (5)	±0.07 (6)	±0.02 (5)

Table 3 Results for 

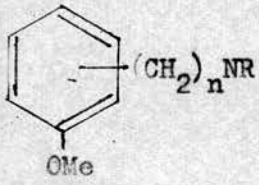
n = 1	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	3.41	1.71	1.80
		± 0.05(4)	±0.03(6)	±0.02(6)
	NEt_2	4.65	4.69	5.37
		± 0.07(6)	±0.04(3)	±0.15(7)

n = 2	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	2.26	0.70	1.40
		± 0.03(5)	±0.02(6)	±0.03(6)
	$\overset{+}{N}Et_3$	4.77	4.00	1.48
		±0.02(4)	±0.13(5)	±0.10(8)

n = 3	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	1.01	2.57	3.85
		±0.03(4)	±0.03(7)	±0.04(5)
	$\overset{+}{N}Et_3$	5.29	5.15	5.02
		±0.05(5)	±0.07(4)	±0.07(5)

Table 4 Results for 

NR	ortho	meta	para
$\overset{+}{N}Me_3$	not prepared	1.12 ± 0.03(4)	1.64 ±0.07(4)
$\overset{+}{N}Et_3$	not prepared	4.67 ±0.07 (6)	4.49 ±0.02(5)

Table 5 Results for 

	NR	ortho	meta	para
n = 1	$\overset{+}{N}Me_3$	2.90 ±0.17(4)	2.89 ±0.03(3)	1.62 ±0.05(4)
	NEt_2	2.14 ±0.11(5)	2.57 ±0.09(4)	2.73 ±0.06(6)
n = 2	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	2.57 ±0.08(4)	2.22 ±0.04(5)	3.13 ±0.14(6)
	$\overset{+}{N}Et_3$	4.44 ±0.05(5)	4.42 ±0.03(4)	3.76 ±0.06(5)
n = 3	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	1.32 ±0.05(3)	1.96 ±0.02(4)	2.80 ±0.09(4)
	$\overset{+}{N}Et_3$	4.32 ±0.06(6)	3.66 ±0.10(6)	4.51 ±0.03(6)

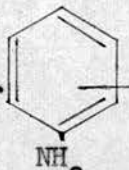
Table 6 Results for  $(CH_2)_n NR$

OH

n = 1	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	2.40	1.67	2.37
		±0.04 (6)	±0.04 (6)	±0.01 (5)
	NEt_2	3.54	3.31	5.90
		±0.06 (4)	±0.13 (5)	±0.03 (8)
	$\overset{+}{N}Et_3$		3.96	
			±0.03 (4)	

n = 2	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	2.42	2.26	0.75
		±0.02 (4)	±0.01 (4)	±0.02 (4)
	$\overset{+}{N}Et_3$	4.27	2.24	2.39
		±0.07 (6)	±0.08 (4)	±0.03 (4)

n = 3	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	1.63	-0.70	1.30
		±0.03 (4)	±0.03 (4)	±0.06 (4)
	$\overset{+}{N}Et_3$	4.43	3.72	3.58
		±0.03 (6)	±0.07 (6)	±0.13 (3)

Table 7 Results for  $(CH_2)_n NR$

n = 1	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	4.05	2.71	3.13
		±0.13(3)	±0.04(6)	±0.08(5)
	NEt_2	3.93	3.47	2.84
		±0.08(6)	±0.02(6)	±0.16(5)

n = 2	NR	ortho	meta	para
	$\overset{+}{N}Me_3$	0.56	0.26	-0.42
		±0.13(5)	±0.02(4)	±0.01(5)
	$\overset{+}{N}Et_3$	4.08	3.91	4.42
		±0.05(4)	±0.10(6)	±0.06(4)

Table 8 Results for  Obtained by Scott (1967).

n	NR = $\overset{+}{N}Me_3$	NR = $\overset{+}{N}Et_3$
1	1.97	4.03 ± 0.05
2	1.05	3.39 ± 0.16
3	0.58	3.99 ± 0.09
4	1.61	5.08 ± 0.04
5	1.25	5.10 ± 0.05

DISCUSSION

Table 9 Base-strengthening and base-weakening effects of substituents in XC_6H_4Y.

X	Y	ortho	meta	para
-Cl	CH_2NMe_2	-0.19	-0.32	-0.13
$-NH_2$	CH_2NMe_2	+0.32	+0.51	+0.87
$-NO_2$	CH_2NEt_2	-0.87	-0.96	-1.11
-Cl	CH_2NEt_2	-0.55	-0.63	-0.49
-OMe	CH_2NEt_2	+0.57	-0.34	-0.09
$-NH_2$	CH_2NEt_2	-0.22	+0.20	+0.61
-Cl	$(CH_2)_2NMe_2$	-0.30	-0.36	-
-Cl	$(CH_2)_2NEt_2$	-0.43	-0.23	-

Table 10 Values for the substituent effect in anilines

Substituent group	ortho	meta	para
$-NO_2$	-4.90	-2.17	-3.64
-Cl	-2.00	-1.30	-0.81
-Br	-2.02	-1.11	-0.71
$-OCH_3$	-0.13	-0.42	+0.67
-OH	+0.10	-0.45	+0.88
$-NH_2$	-0.15	+0.26	+1.46

These are calculated from pKa values quoted by Braude and Nachod (Ch 14) and listed in Appendix I.

Relationships between structure, pKa and electron distribution.

The base-strengthening or base-weakening effects of the substituent groups are indicated by the difference in pKa between the substituted and the corresponding unsubstituted amine. They are shown in table 9, calculated from the pKa results of table 1. These can be compared with the results for the corresponding anilines quoted by Braude and Nachod (Ch.14) which are shown in table 10. Both sets of results are presented graphically in figs. 7 and 8. Results with the benzyldimethylamines show the same effects as the diethylamines, but are not plotted because there are very few results.

The base-strengthening and base-weakening effects of the substituents should be correlated with the electron releasing and withdrawing properties of the groups. Fig.7 shows a marked upward trend in the anilines on going from nitro to amino. The results for the benzyldiethylamines show similar effects, although the differences are smaller because of the interposed methylene group. In table 11, the groups are arranged in order of increased ability to release electrons, to compare the effects in the anilines with those in the benzyldiethylamines.

Apart from the ortho compounds, the same order is shown in each series, except that the effects of the p-methoxy and m-amino groups are different in one series from what they are in the other; they have values of + 0.67 and + 0.26 respectively in the anilines, and - 0.09 and + 0.20 respectively in the benzyldiethylamines.

Any steric effects of ortho groups are likely to be greater in the anilines than in the benzyl diethylamines because, in the anilines, the substituent

FIGURE 7

Base-strengthening and base-weakening effects in substituted anilines. (Red, blue, and green points represent ortho, meta, and para compounds respectively).

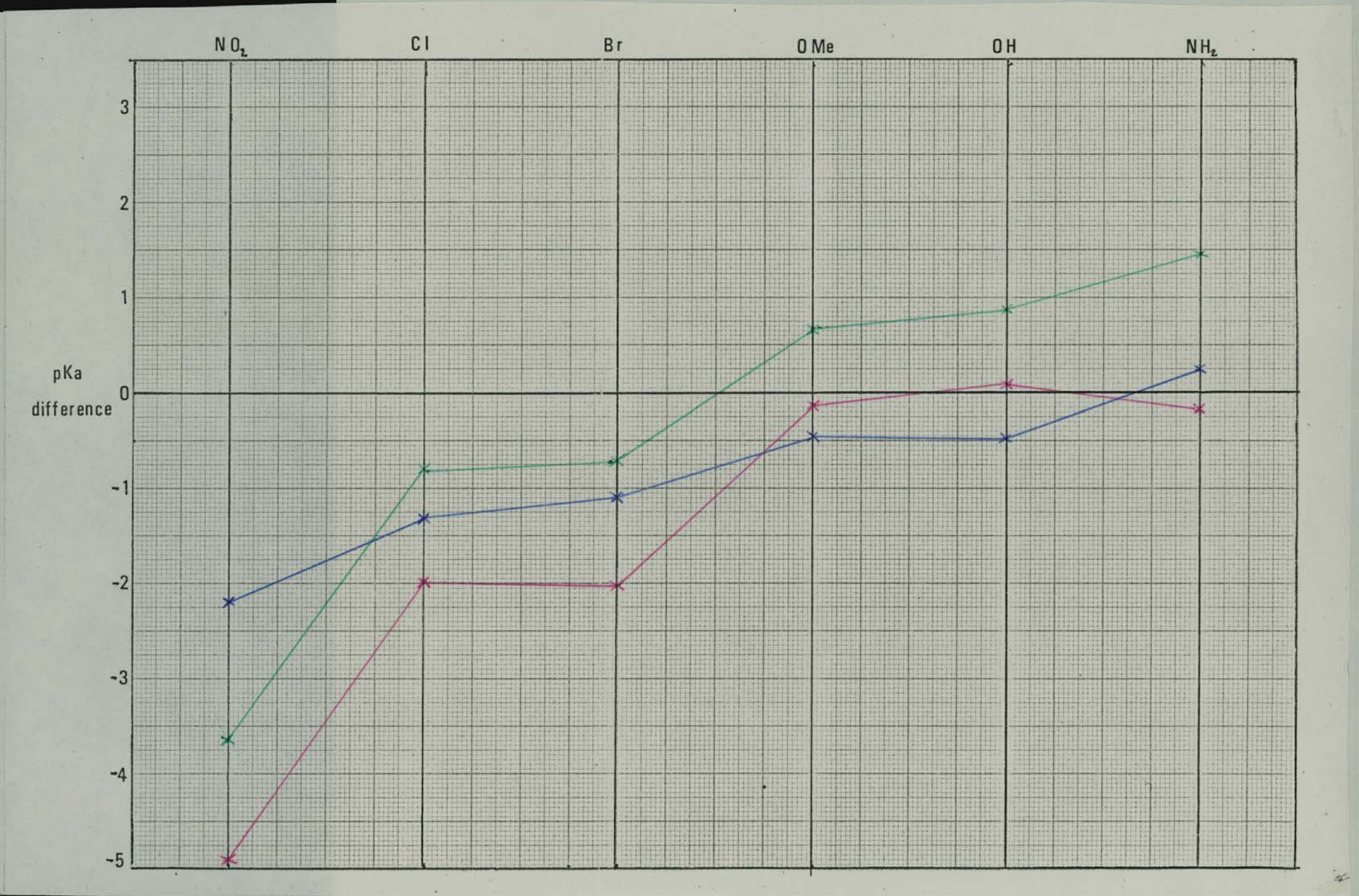


FIGURE 8

Base-strengthening and base-weakening effects in $X.PhCH_2NEt_2$ (Red, blue, and green points represent ortho, meta, and para compounds respectively).

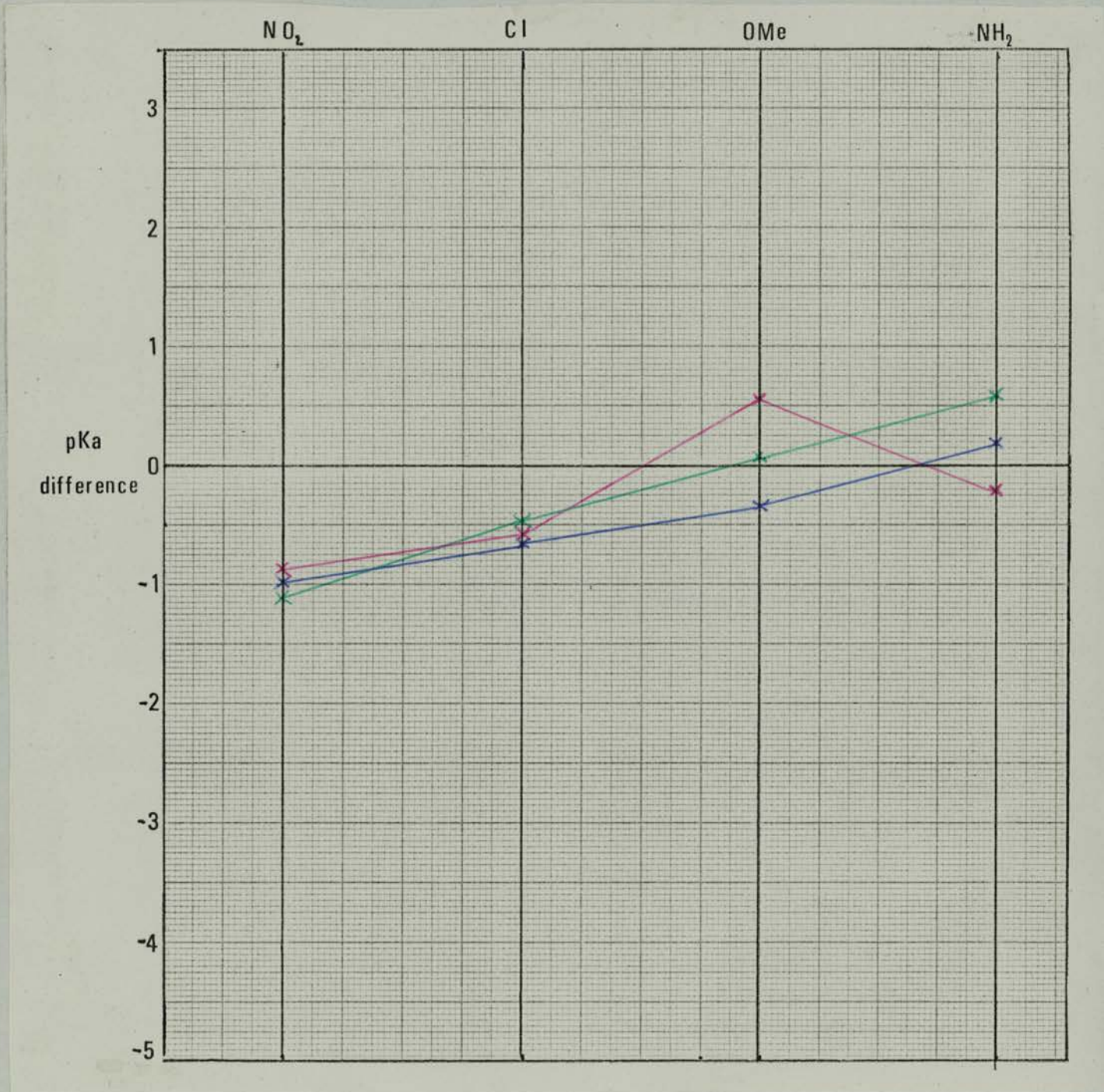


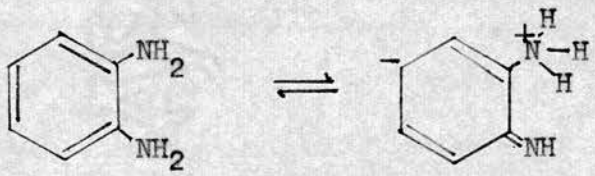
Table 11 Comparison of substituent effects in aniline and benzyl diethylamine.

Anilines	Base-strengthening effect	Benzyldiethylamines	Base-strengthening effect
o-NO_2	-4.90		
p-NO_2	-3.64	p-NO_2	-1.11
m-NO_2	-2.17	m-NO_2	-0.96
o-Br	-2.02	o-NO_2	-0.87
o-Cl	-2.00		
m-Cl	-1.30	m-Cl	-0.63
m-Br	-1.11	o-Cl	-0.55
p-Cl	-0.81	p-Cl	-0.49
p-Br	-0.71		
m-OH	-0.45		
m-OMe	-0.42	m-OMe	-0.34
o-NH_2	-0.15	o-NH_2	-0.22
o-OMe	-0.13		
o-OH	+0.10		
m-NH_2	+0.26	p-OMe	-0.09
p-OMe	+0.67	m-NH_2	+0.20
p-OH	+0.88	o-OMe	+0.57
p-NH_2	+1.46	p-NH_2	+0.61

Table 12 Estimated values for the substituent effect in hydroxy and bromo benzyldiethylamines (calculated from Table 11).

Substituent	Base-strengthening effect
o-OH	+0.04
m-OH	-0.36
p-OH	+0.10
m-Br	-0.58
p-Br	-0.45

group is closer to the nitrogen. These effects may be responsible for the irregularities which occur in the ortho series. For example, the low pKa of o-nitroaniline is partly due to the short distance over which the inductive effect of the nitro group operates, and partly due to direct interaction, both steric and hydrogen bonded, between the nitro and amino groups. Likewise, o-phenylene diamine is a weaker base than would be expected from the mesomeric effect alone, due to hydrogen bonding, which can be represented by:



+ other forms

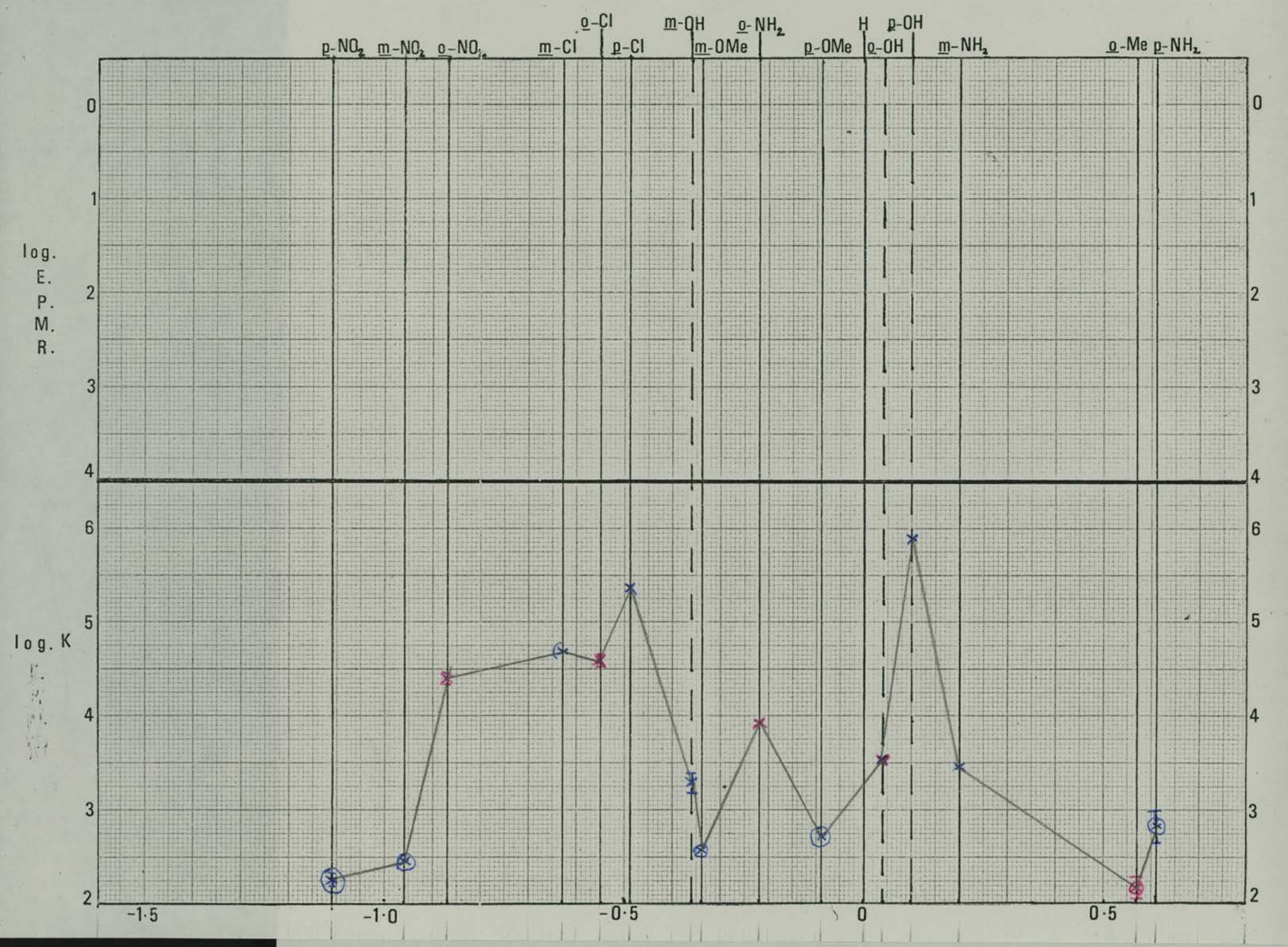
Thus, in the benzyl compounds, there should be less anomalies with the ortho substituted analogues, unless there is a possibility of cyclic interaction, which may be responsible for the high pKa of o-methoxybenzyldiethylamine.

Unfortunately, the pKa values of the bromo and hydroxy substituted benzyldiethylamines were not determined. From the position of the substituent in the results with the anilines, the possible position in the benzyldiethylamine series has been calculated by proportion, and the values shown in table 12. This method is probably only qualitatively valid for the meta and para compounds, and the result for o-hydroxybenzyldiethylamine must be treated with great reserve, because, almost certainly, there is hydrogen bonding in o-aminophenol.

The pKa differences for the benzyldiethylamines, shown in tables 11 and 12, have been used as a measure of electron releasing ability of the substituents, and will be referred to as the substituent effect.

FIGURE 9

Variation of log. K with substituent constant in $X.PhCH_2NEt_2$ (Red points are ortho compounds, circled points are partial agonists).



Relationships between structure and affinity.

Figs. 9 to 11 show the results for the diethylamino and triethylammonium compounds. The log. affinities of the partial agonists and antagonists and the log. equipotent molar ratios of the agonists have been plotted against the substituent effect.

Affinities of benzyldiethylamines (Fig. 9)

Some of the compounds are antagonists and some are partial agonists, as shown below.

Antagonists	log K	Partial agonists	log K
o-nitro	4.41	m-nitro	2.46
o-chloro	4.65	p-nitro	2.27
m-chloro	4.69	m-hydroxy	3.31
p-chloro	5.37	m-methoxy	2.57
o-amino	3.93	p-methoxy	2.73
o-hydroxy	3.54	o-methoxy	2.14
p-hydroxy	5.90	p-amino	2.84
m-amino	3.47		

From the graph there is no evident correlation between affinity and electronic effect in the series. Striking features are the high affinity of p-hydroxybenzyldiethylamine, and the low affinity of the methoxy compounds and the m and p - nitrobenzyldiethylamines.

It is also remarkable that most of the partial agonists have low affinity compared with the antagonists. In three instances the quaternary triethylammonium compounds were tested, and invariably had higher affinity and less efficacy than the diethylamino compounds; thus, in the m-nitro compounds the difference in affinity was 1.9 log units, with the p-nitro

compounds it was 0.8 log units, and with the m-hydroxy compounds it was 0.6 log units. In each instance the addition of the extra ethyl group converted a partial agonist into a pure antagonist. These effects are very similar to those reported by Scott (1967) with similar pyridyl derivatives.

Affinities of benzyltrimethylammonium salts

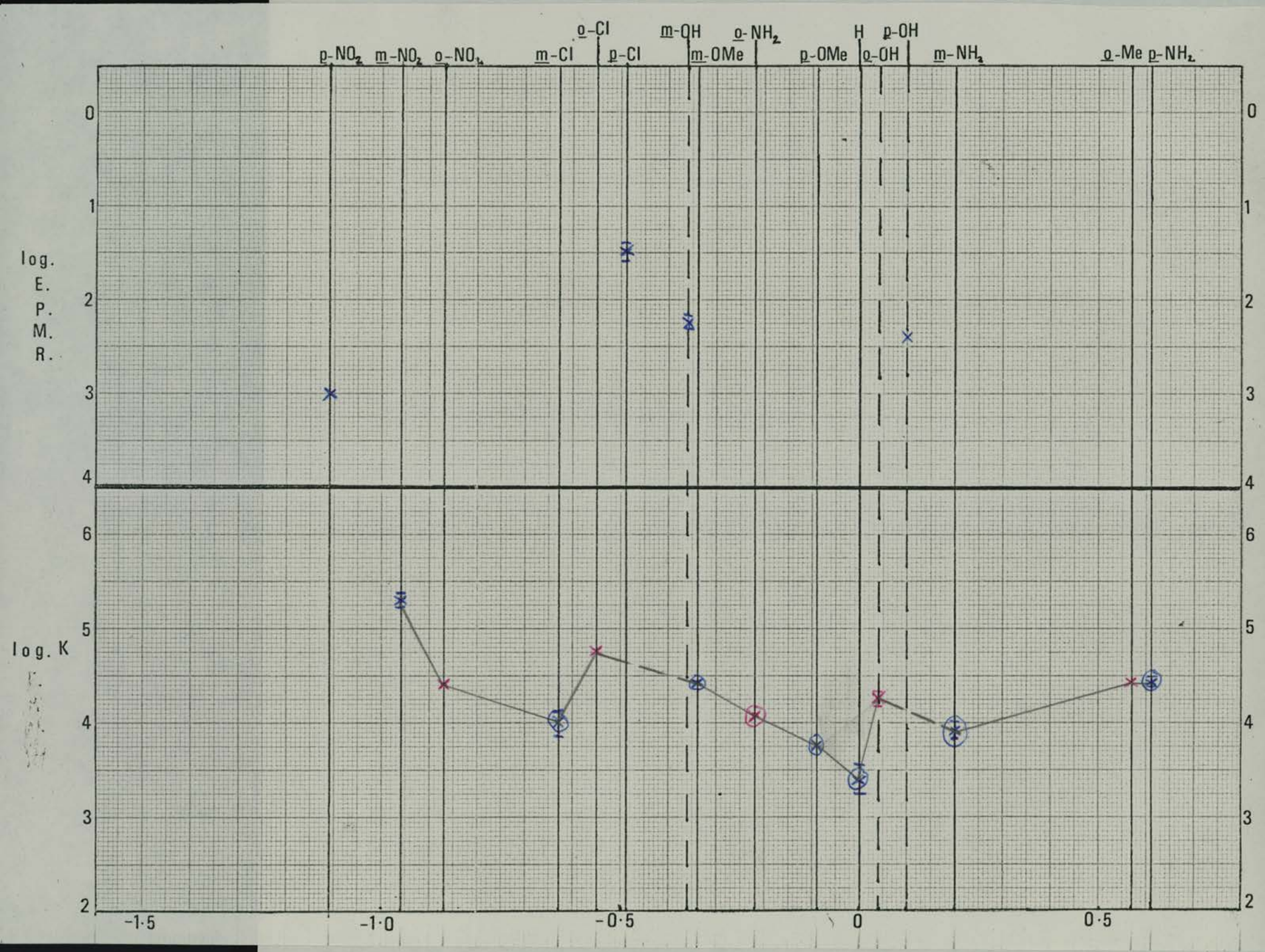
A few of these were partial agonists and one was an antagonist.

Antagonist	log K	Partial agonists	log K
o-amino	4.05	o-nitro	3.32
		o-chloro	3.41
		o-methoxy	2.90
		p-amino	3.13

It was remarkable that, although the o-amino, o-methoxy, and p-amino trimethylammonium compounds had slightly higher affinity than their diethyl analogues, the o-nitro and o-chloro compounds had much smaller affinities than the corresponding diethylamino compounds, the differences being more than one log unit. This suggests that the position of the onium group relative to the receptor is different in the two types of compound, the nitro and chloro on one hand, and the amino and methoxy on the other.

FIGURE 10

Variation of log. K and log. E.P.M.R. with substituent constant in $X.Ph(CH_2)_2NEt_3$. (Red points are ortho compounds, circled points are partial agonists).



Affinities of phenethyltriethylammonium salts (Fig.10)

Most of these compounds are agonists or partial agonists, as shown:

Agonists	Partial agonists	Antagonists
p-nitro	m-chloro	o-nitro
	m-methoxy	m-nitro
p-chloro	p-methoxy	o-chloro
m-hydroxy	o-amino	o-methoxy
p-hydroxy	m-amino	o-hydroxy
	p-amino	
	unsubstituted	

From the results obtained with the partial agonists and antagonists, whose affinity can be measured, the introduction of more or less any group into the benzene ring increases affinity regardless of its effects on electron distribution.

Affinities of phenethyltrimethylammonium salts

The only partial agonist was the p-methoxy compound which had a log affinity of 3.13. This is 0.6 log units less than the affinity of its triethylammonium analogue.

Affinities of phenylpropyltriethylammonium salts (Fig.11)

In this series there are no pure agonists, and the others are as shown:

Partial agonists	Antagonists
o-chloro	o-methoxy
m-chloro	o-hydroxy
p-chloro	

FIGURE 11

Variation of log. K with substituent constant in $X.Ph(CH_2)_3NEt_3$
(Red points are ortho compounds, circled points are partial agonists).

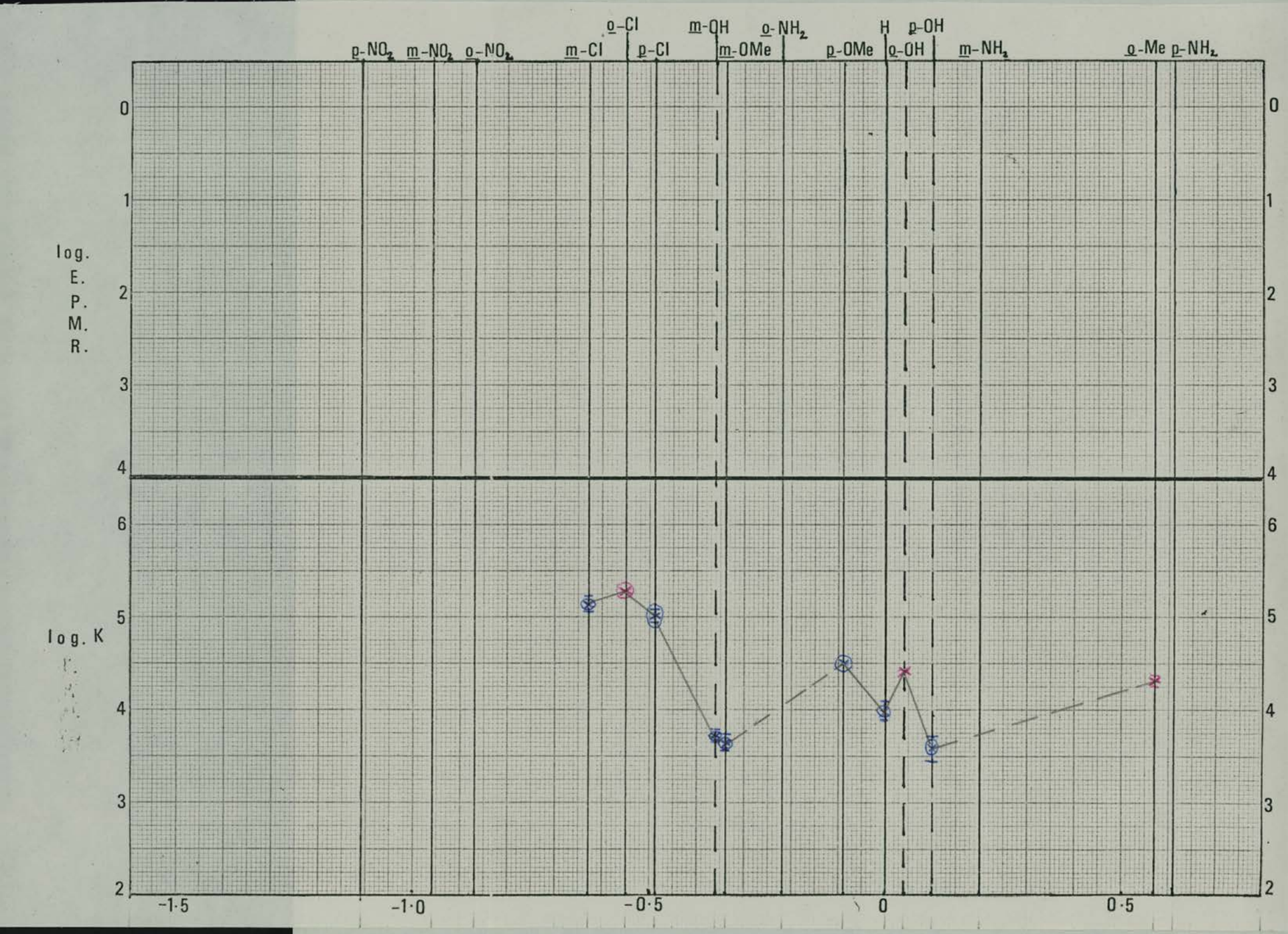
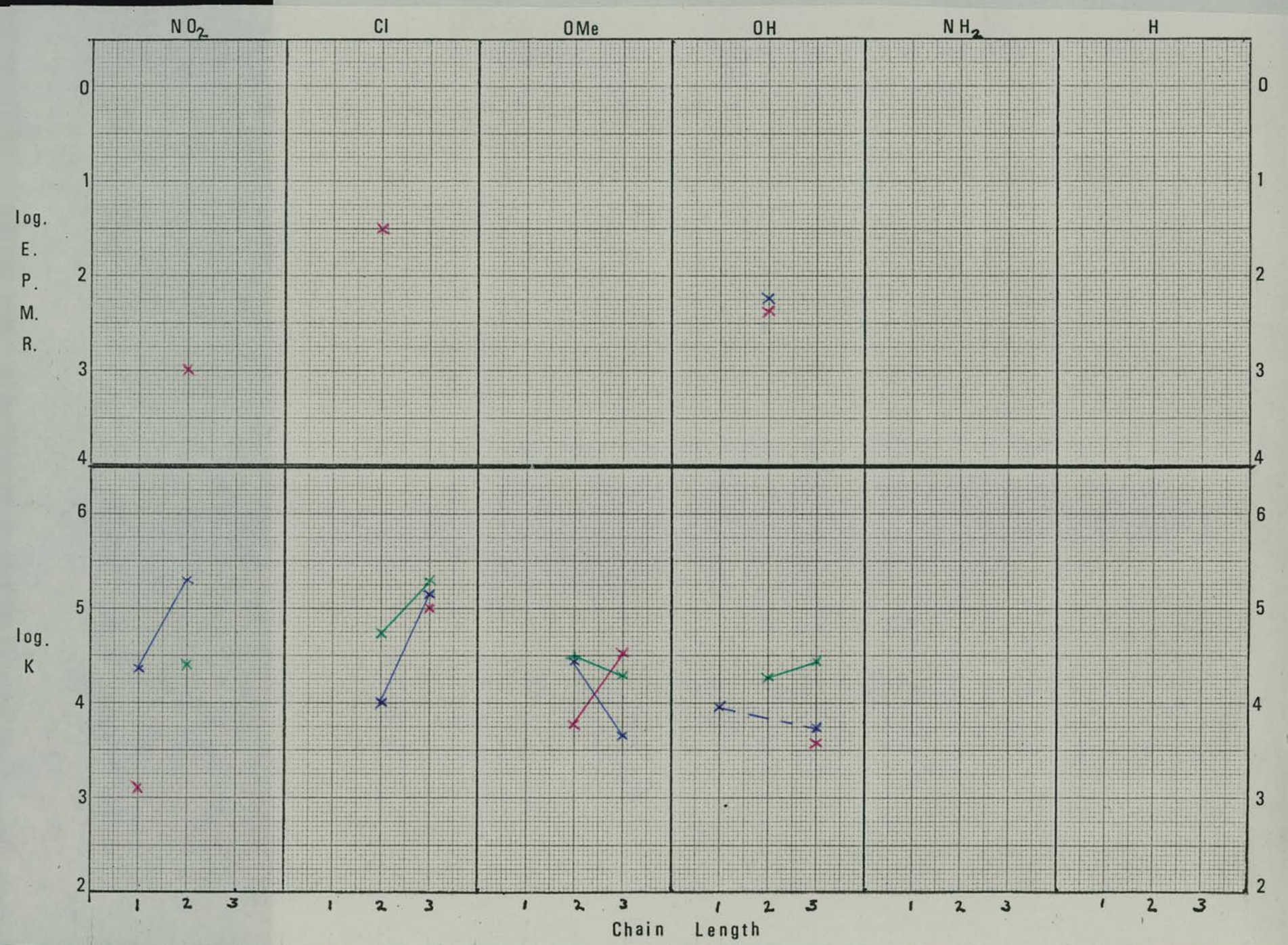


FIGURE 12

Variation of log. K and log. E.P.M.R. with chain length in $X.Ph(CH_2)_n\overset{+}{N}Et_3$. (Green, blue, and red points represent ortho, meta, and para compounds respectively).



Partial agonists

m-methoxy

p-methoxy

m-hydroxy

p-hydroxy

unsubstituted

The situation is very similar to that in the phenethyl series, although the substituted compounds have both higher and lower affinities than the unsubstituted analogue. There is no discernable correlation between affinity and electron withdrawing or donating effects of the substituent groups.

Affinities of phenylpropyltrimethylammonium salts

All those made were pure agonists, but the nitro and amino compounds, some of which were partial agonists and antagonists in the benzyl series, were not made. It is possible, therefore, that they are not all pure agonists, although there is a slight suggestion that they are, because the chloro and methoxy compounds are pure agonists, whereas some of these were partial agonists in the benzyl series.

Relationship between chain length and affinity (Fig.12)

The effect of chain length on affinity appears to be variable, although it is difficult to make a systematic comparison, because very few benzyltriethylammonium compounds have been tested.

The reason for this is not clear; it does not seem to depend on the type of substituent.

The measurements of affinity, therefore, are disappointing in that I have failed to observe any correlation between binding and effects on electron distribution. The introduction of substituents, however, alters the size of the molecule as well as the electron distribution, and this could also affect binding.

With the particular groups selected, increased ability to withdraw electrons is closely associated with increased size. The order in which they have been arranged according to their effects on electron distribution, is very similar to their order when arranged according to size. For example, the most electron withdrawing groups, nitro, chloro, and bromo, are also the biggest groups. The most electron releasing, hydroxy and amino, are the smallest groups.

The failure to obtain any direct correlation between affinity and electron withdrawing ability is also, therefore, a failure to obtain a direct correlation with the size of the group. It is probably quite unjustifiable to regard the effects of a group on affinity as being due only to one or other of these properties, and one possible explanation of the apparent absence of dependance of affinity on either of these properties, is that both are involved but act in opposite directions. For example, there appears to be a slight tendency, shown in figs. 10 and 11 but not fig.9, for higher affinity to be associated with electron withdrawing ability. It might be argued that increased binding due to the electronic effects of these groups is being offset by the increased size of the groups; it could equally be argued that the beneficial effects of increased size are offset by the electronic effects.

FIGURE 13

Variation of log. K with position of substitution in $X.PhCH_2NEt_2$. (Circled points are partial agonists).

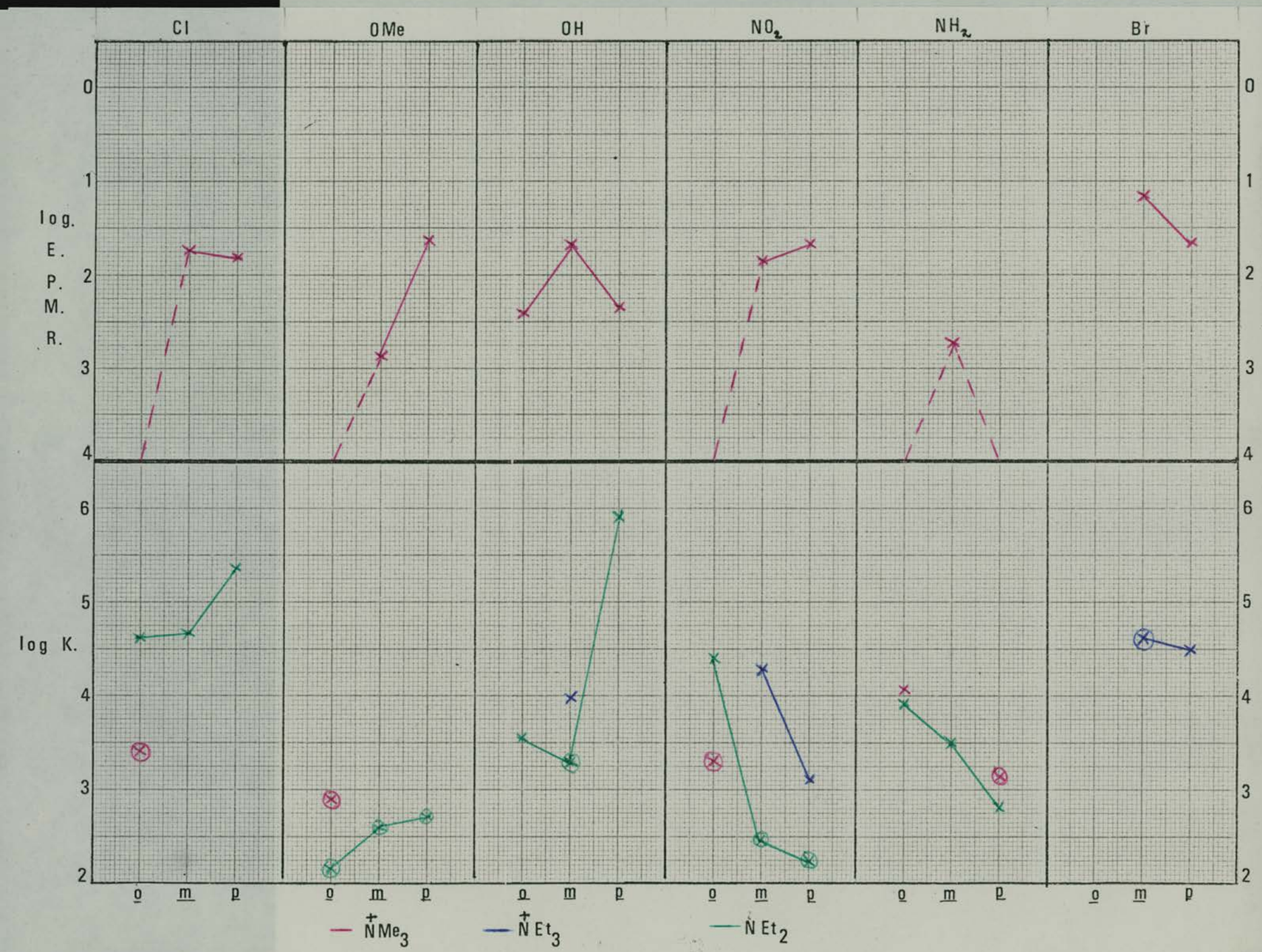


FIGURE 14

Variation of log. K and log. E.P.M.R. with position of substitution in $X.Ph.(CH_2)_2\overset{+}{N}Et_3$. (Circled points are partial agonists).

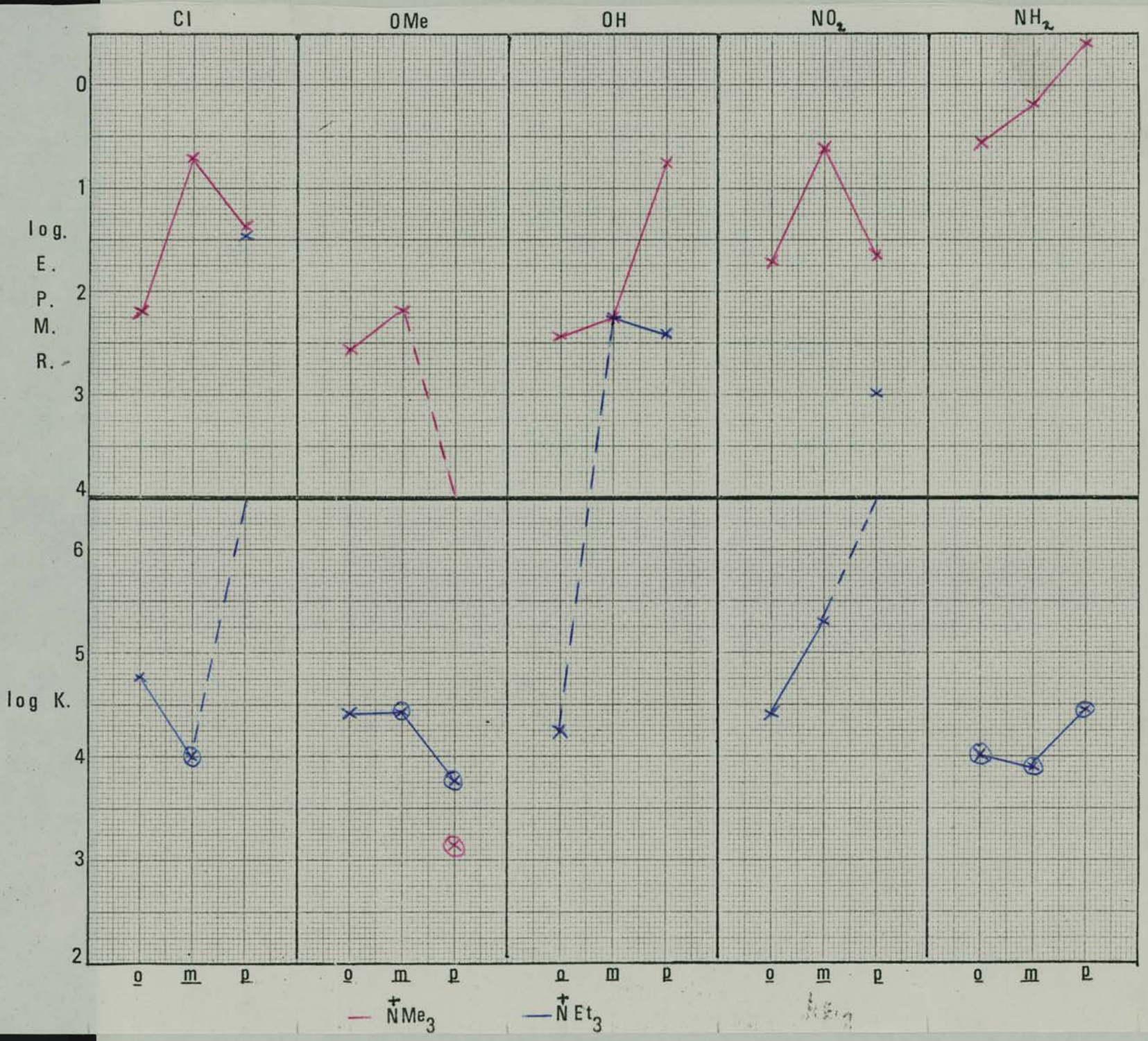


FIGURE 15

Variation of log. K with position of substitution in $X.Ph(CH_2)_3\overset{+}{N}Et_3$.
(Circled points are partial agonists)

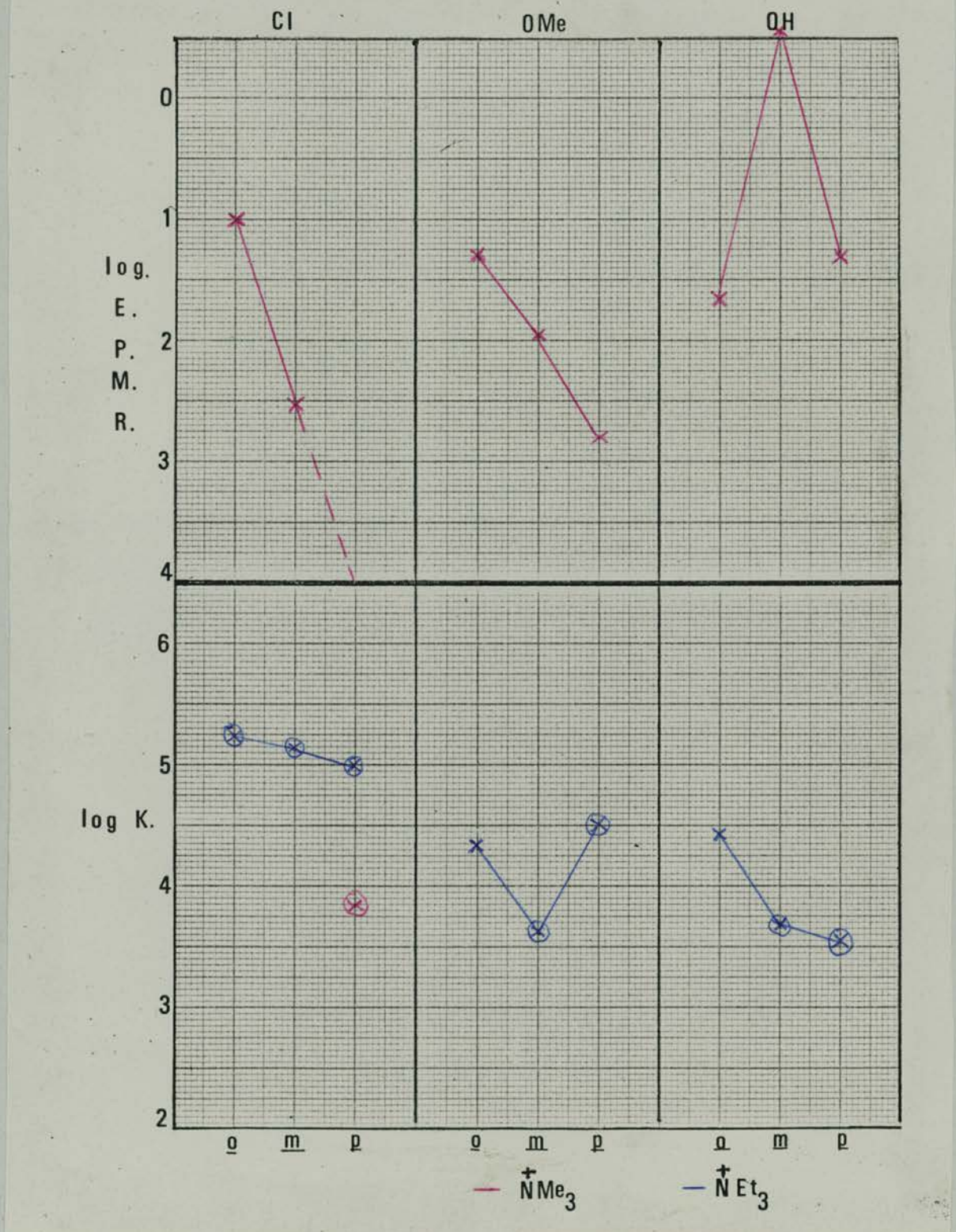


Table 13 Compounds with high affinity

compound	log K
p-$HOC_6H_4CH_2NEt_2$	5.50
p-$ClC_6H_4CH_2NEt_2$	5.37
m-$O_2NC_6H_4(CH_2)_2\overset{+}{N}Et_3$	5.30
o-$ClC_6H_4(CH_2)_3\overset{+}{N}Et_3$	5.29
m-$ClC_6H_4(CH_2)_3\overset{+}{N}Et_3$	5.19
p-$ClC_6H_4(CH_2)_3\overset{+}{N}Et_3$	5.02
o-$ClC_6H_4(CH_2)_2\overset{+}{N}Et_3$	4.77
m-$ClC_6H_4CH_2NEt_2$	4.69
m-$BrC_6H_4CH_2\overset{+}{N}Et_3$	4.67
o-$ClC_6H_4CH_2NEt_2$	4.65

Values underlined are log affinity constants of partial agonists.

The effects of the group on electron distribution alone might be studied by comparing the affinities of the ortho, meta and para isomers of each series. As can be seen from figs. 13, 14, and 15, there is no obvious trend with these isomers. However, even with these isomeric compounds, it is not really correct to assume that the electronic effect is the only one operating. The binding of each of the compounds to the receptor will be different, because the relative position of the substituent and the onium group will not be the same.

In the absence of any regular effects of substituents on affinity it is impossible to come to any conclusions about what chemical factors might be important. If one looks at the formulae of the compounds with the highest affinity (Table 13), the most striking feature is the high incidence of chloro compounds, but the position of the substituent does not seem to be important.

Indeed, with the exception of p-hydroxybenzyldiethylamine, whose large affinity constant makes it unique among the compounds studied, chloro, nitro, and bromo substitution appears to confer high affinity on the molecules. The high affinity of p-hydroxybenzyldiethylamine is particularly remarkable in view of the only moderate affinity of other hydroxy compounds. Because affinity usually increases when changing from diethylamino to triethylammonium compounds, it would be extremely interesting to test p-hydroxybenzyltriethylammonium, which should be a very potent antagonist.

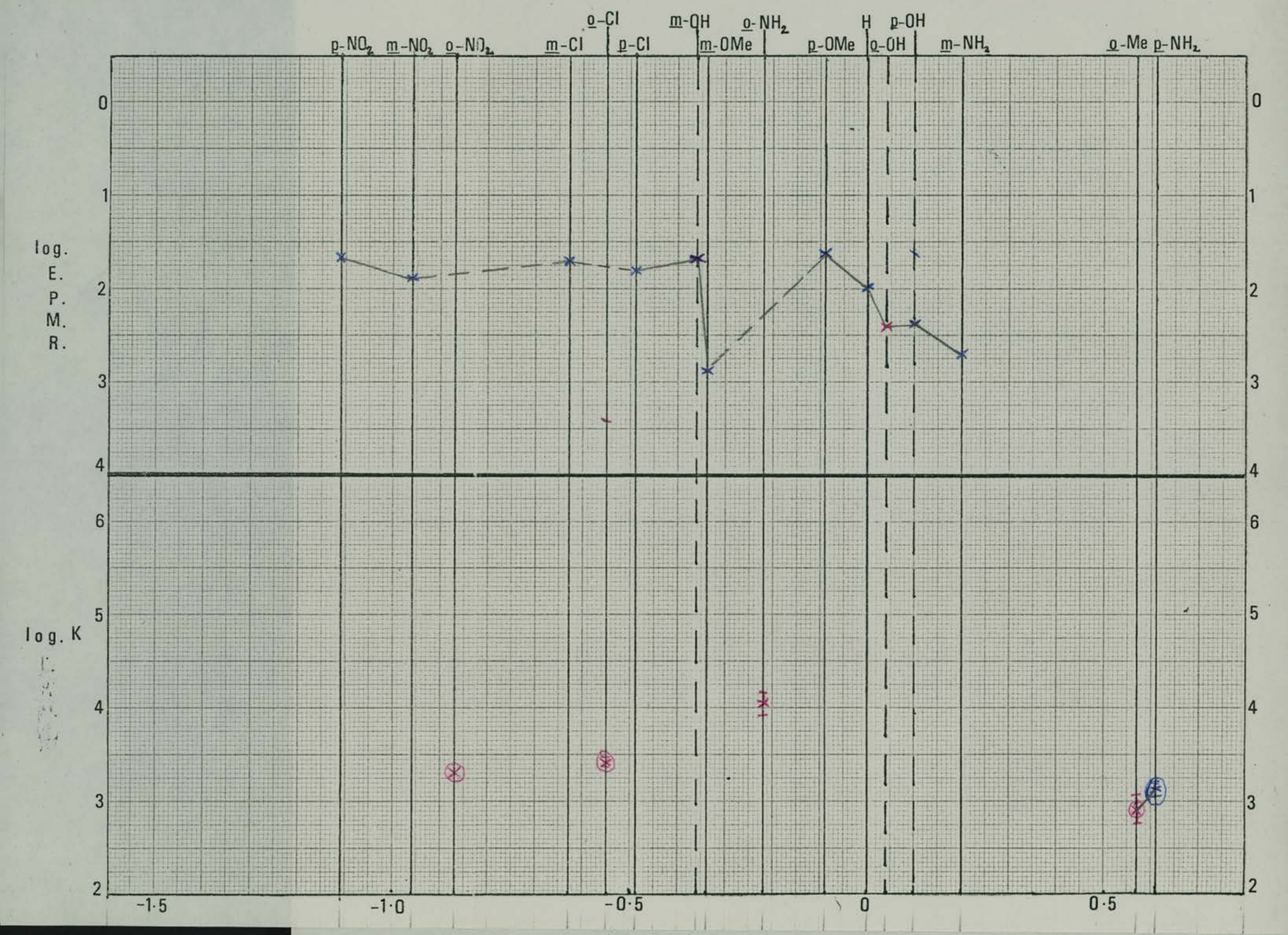
Relationships between structure and efficacy

Originally it was intended to use what was known about the relationships between structure and affinity to deduce the effects of changes in structure on efficacy. The effects of changes in structure on affinity, however, do not seem to be simply related to the parameters we have considered, electron distribution, number of methylene groups in the side chain, and size of the substituent group. Although the trimethylammonium compounds would be expected to have affinities less than those of their triethylammonium analogues, perhaps by up to one log unit, it is unjustifiable to assume that this expectation will always be correct. In fact, where it is possible to compare the affinities of trimethylammonium compounds with diethylamino or triethylammonium compounds, it is quite clear that not enough is yet known to predict the affinities of the trimethylammonium salts. Although the o-methoxy and o- and p-amino benzyltrimethylammonium compounds had slightly higher affinity than the diethylamino analogues, the o-nitro and o-chloro benzyltrimethylammonium compounds had very much smaller affinity than their diethylamino analogues, the difference being more than one log unit.

In view of this it is quite unjustifiable to attempt to make a quantitative estimate of changes in efficacy by comparing equipotent molar ratios of trimethylammonium compounds with changes in affinity in their triethylammonium or diethylamino analogues. Qualitative observations can be made, however, because small changes in structure alter the efficacy of some trimethylammonium compounds so drastically that they become partial agonists or antagonists. Also, some changes convert diethylamino and triethylammonium compounds from antagonists to partial agonists, and even to agonists.

FIGURE 16

Variation of log. E.P.M.R. and log. K with substituent constant in $X.PhCH_2\overset{+}{N}Me_3$. (Red points are ortho compounds, circled points are partial agonists)



Figs. 16 to 18 show the results for the trimethylammonium compounds. The log equipotent molar ratios of the agonists and the log affinities of the partial agonists and antagonists have been plotted against the substituent effect.

Activities of benzyltrimethylammonium salts (Fig.16)

Most of these were agonists; there were, however, four partial agonists and one antagonist, as described on page 25. For convenience these are repeated below:

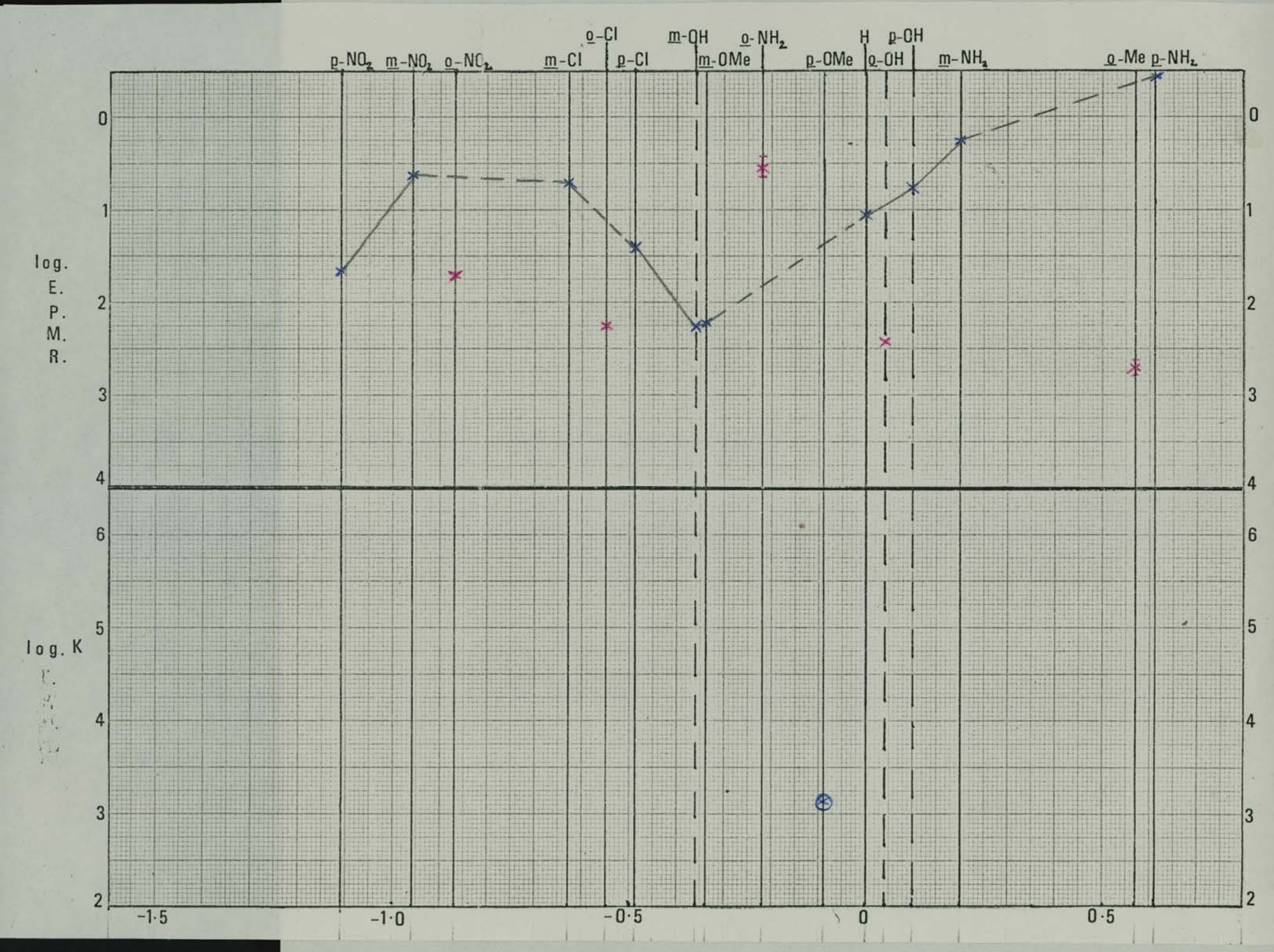
Antagonist	log K	Partial agonists	log K
o-amino	4.05	o-nitro	3.32
		o-chloro	3.41
		o-methoxy	2.90
		p-amino	3.13

There is no obvious correlation between activity and substituent effect except that o- substituted compounds have low efficacy: except o-hydroxybenzyltrimethylammonium they are all partial agonists or antagonists. This effect may be associated with the size of the substituent group, because the o-hydroxy compound, which has a small substituent, is a pure agonist. If it is the size of the group which reduces efficacy, the o-amino compound ought also to be a pure agonist, but it is an antagonist. The p-amino isomer, however, is a partial agonist, so possibly the amino group itself reduces efficacy in the o- and p positions.

With the diethylamino compounds (already discussed on page 24), there are also differences in efficacy, because some of the compounds are partial agonists.

FIGURE 17

Variation of log. E.P.M.R. and log. K with substituent constant in $X.Ph(CH_2)_2NMe_3$. (Red points are ortho compounds, circled points are partial agonists).



Activity of phenethyltrimethylammonium salts (Fig.17).

These are all agonists except the p-methoxy compound which is a partial agonist (page 26).

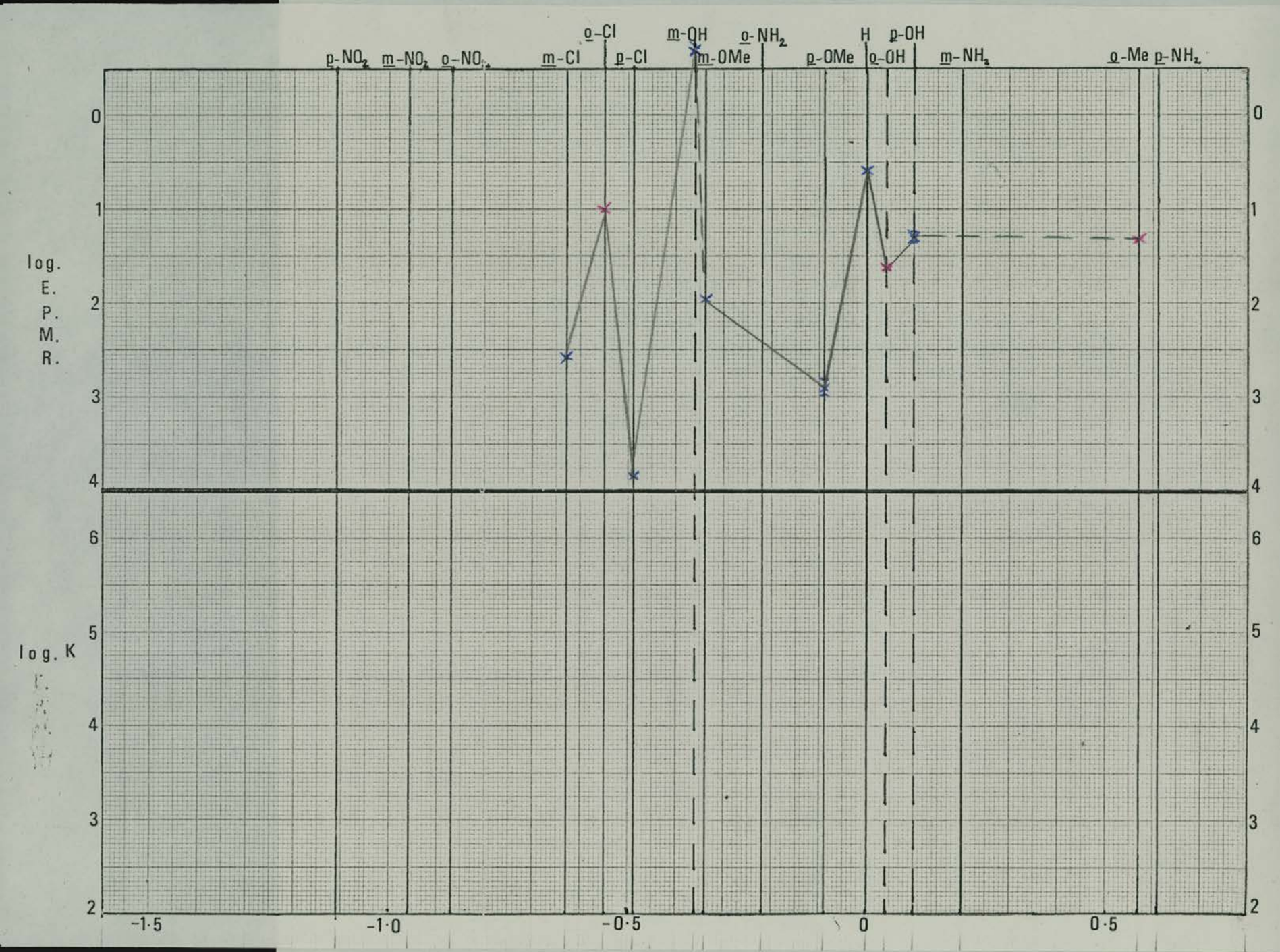
The ortho compounds again have lower activity than the meta and para isomers, though the difference is not so marked as with the benzyl series. As all the ortho substituted triethylammonium analogues have much the same affinity as their meta and para isomers, it seems likely that ortho substituents reduce efficacy, with the exception of the o-amino group. As already discussed (page 31), it is probably not valid to compare the affinities of triethylammonium compounds and their trimethylammonium analogues in this way. However, although it is not correct to try to obtain quantitative information about efficacy for individual compounds, this comparison seems reasonable since four pairs of compounds are involved.

The graph appears to indicate two trends, a decline in activity from left to right, followed by a rise. This could be explained by a rise in efficacy, coupled with a decline in affinity, from right to left. For example, possibly the nitro and chloro compounds have high activity because they have high affinity and moderate efficacy, and the meta and para amino compounds have high activity because they have high efficacy and moderate affinity.

The low value obtained for the activity of m-hydroxyphenethyl trimethylammonium compared with that of Erspamer and Glasser (1960) is difficult to understand. They gave a value of 0.20-0.25 for its equipotent molar ratio relative to acetylcholine. This differs from the value I obtained by a factor of about 200.

FIGURE 18

Variation of log. E.P.M.R. with substituent constance in $X.Ph(CH_2)_3\overset{+}{N}Me_3$. (Red points are ortho compounds, circled points are partial agonists).



Activity of phenethyltriethylammonium salts (Fig.11)

All the ortho substituted compounds except the o-amino analogue, are pure antagonists, whereas almost all the other compounds are partial agonists or agonists (page 26). This is further indication that an ortho substituent reduces the efficacy of the molecule.

The p-nitro, p-chloro, and m and p-hydroxy compounds are agonists, and so these groups confer efficacy on the molecule. Since p-nitro appears at the left of the graph, and p-hydroxy appears at the right, this observation does not give support to the suggestion that efficacy is increased from left to right of the graph.

Activity of phenylpropyltrimethylammonium compounds (Fig.18)

The remarkably high activity of the m-hydroxy compound was completely unexpected. This is an extremely potent compound being about 40 times as active as nicotine. All the other substituted compounds in this series are less active than the unsubstituted analogue, but there does not appear to be any discernable pattern. The ortho compounds do not show particularly low activity.

In the phenylpropyltriethylammonium series all the compounds studied were partial agonists except the o-hydroxy and o-methoxy analogues which were antagonists. (page 26).

FIGURE 19

Variation of $_{+}$log. E.P.M.R. and log. K with chain length in o-X.Ph(CH_2)nNMe_3. (Circled points are partial agonists).

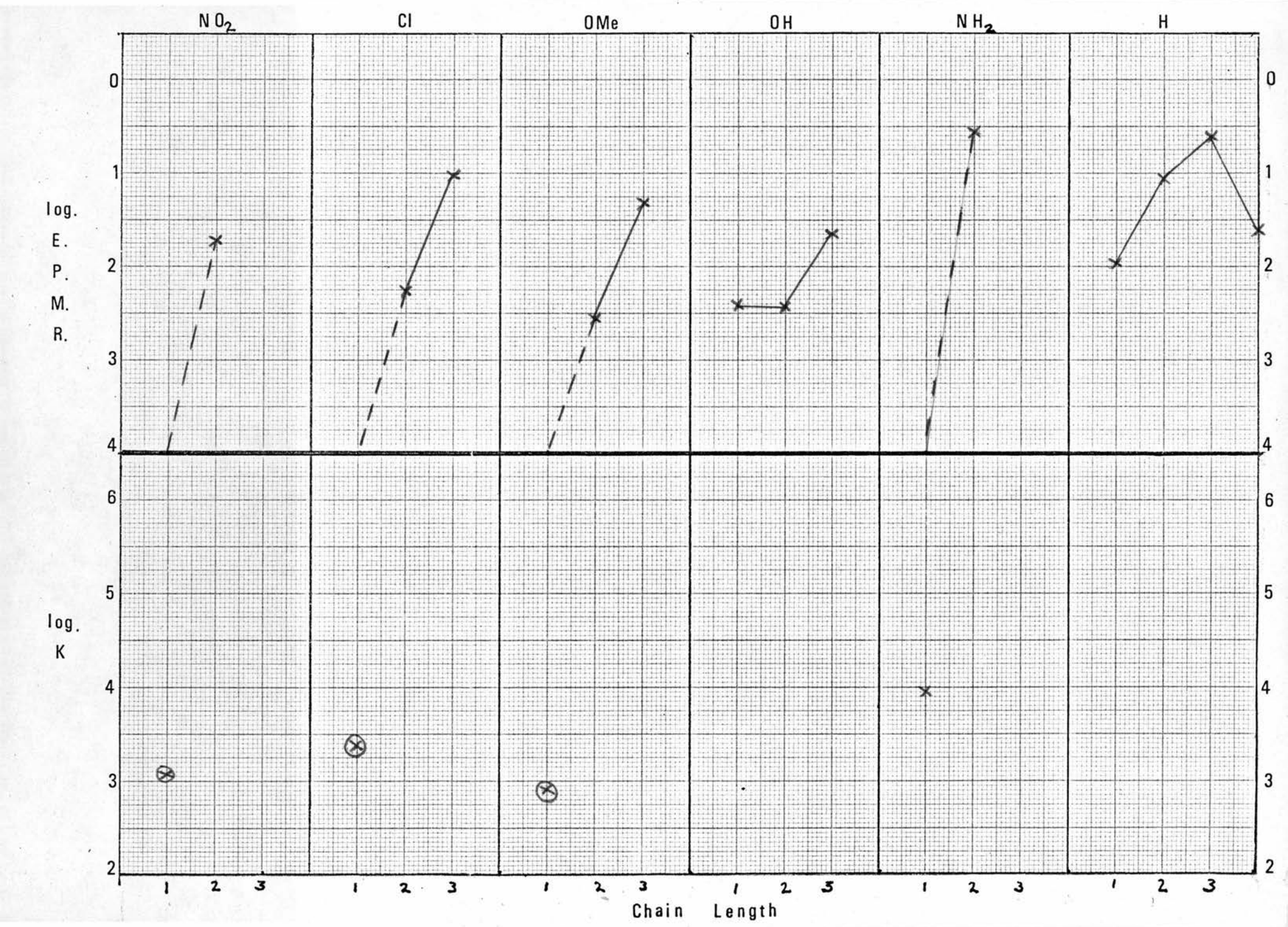


FIGURE 20

Variation of log. E.P.M.R. with chain length in m-X.Ph$(CH_2)_n\overset{+}{N}Me_3$.

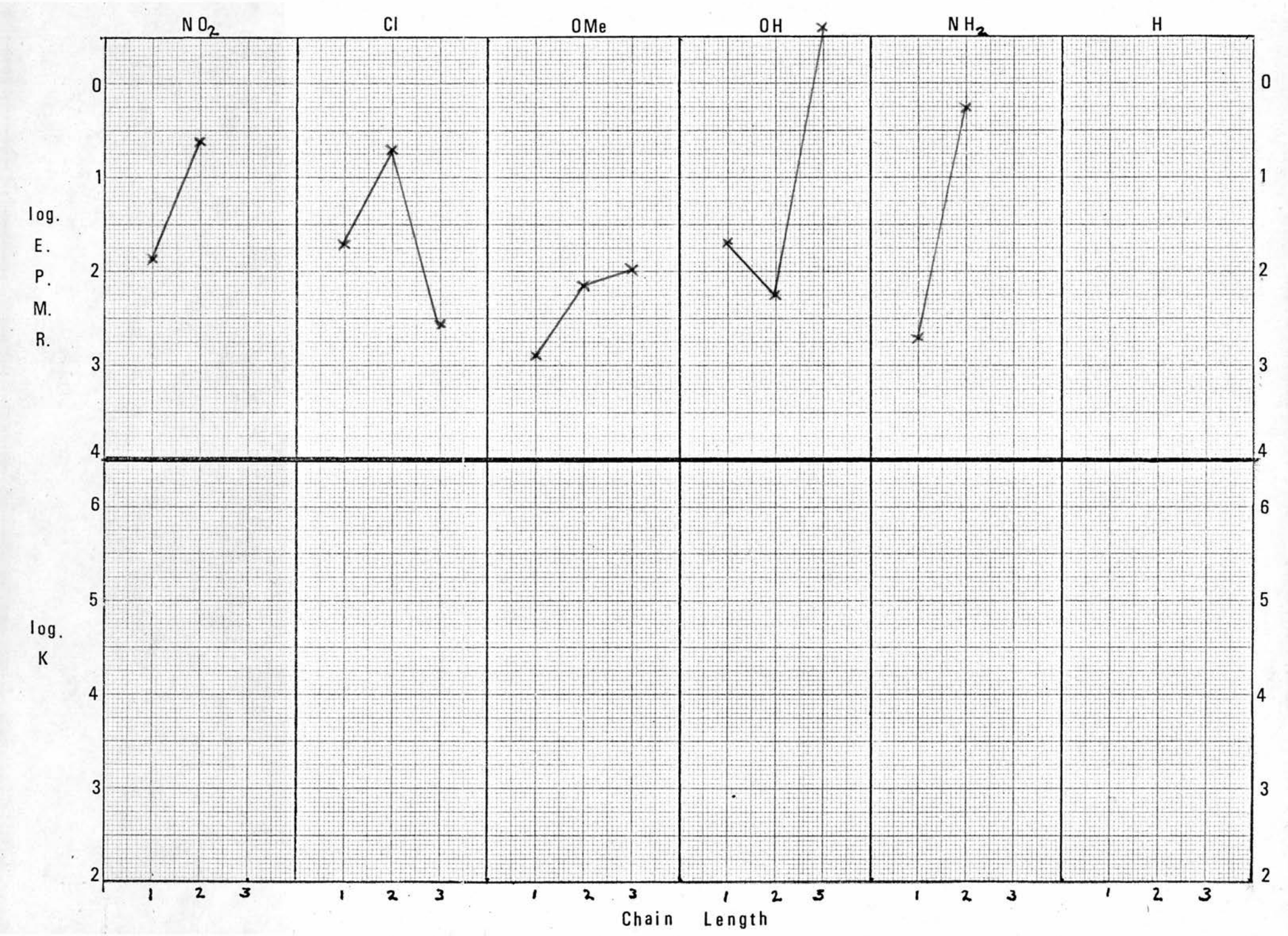
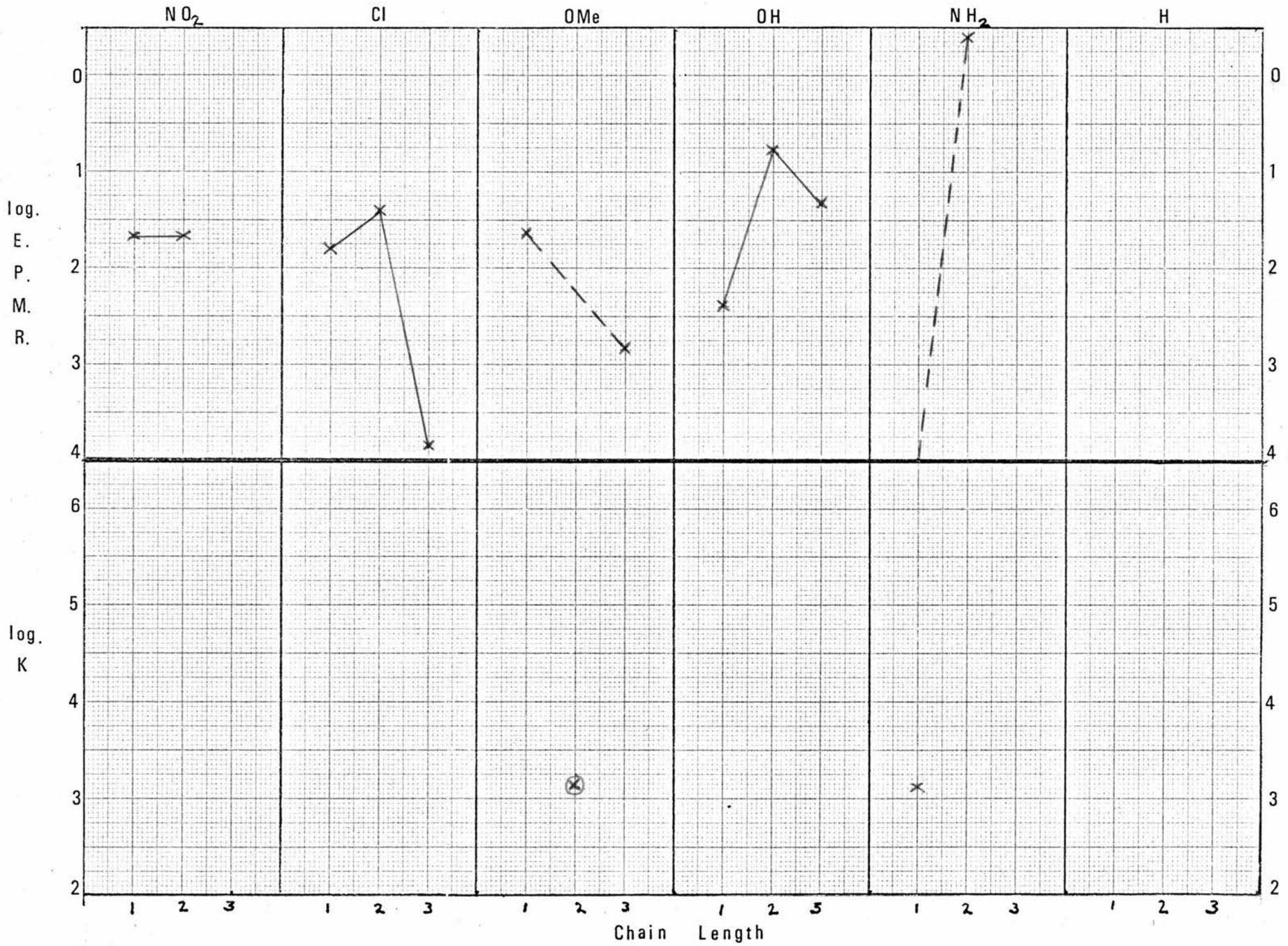


FIGURE 21

Variation of log. E.P.M.R. and log. K with chain length in p-X.Ph$(CH_2)_n\overset{+}{N}Me_3$. (Circled points are partial agonists).



Relationship between chain length and activity

Figs. 19, 20, and 21 show the variation of activity of the ortho, meta, and para substituted compounds with the number of methylene groups in the side chain. The unsubstituted analogues are plotted on the same graph as the ortho compounds.

Ortho substituted compounds

The change from partial agonist to agonist on lengthening the chain from benzyl to phenethyl has already been discussed. The phenylpropyl compounds that have been studied are more active than their corresponding phenethyl homologues. The unsubstituted analogues also show maximum activity in the phenylpropyl series.

Meta substituted compounds

In almost every series the phenethyl compound is more active than the benzyl compound. Addition of a further methylene group, however, may increase or decrease activity.

Para substituted compounds

With the exception of the methoxyphenethyl analogue the compounds with two methylene groups in the sidechain are the most active ones.

From these observations, it might be concluded that the distance between the onium group and the substituent in the benzene ring is important for activity. As the substituent position is altered from ortho to para, the more active compounds change from the phenylpropyl to the phenethyl series. Whether this effect is due to change in efficacy or affinity is not clear.

Table 14 Agonists in order of activity.

Compound	log E.P.M.R.
m-$HOC_6H_4(CH_2)_3\overset{+}{N}Me_3$	-0.70
p-$H_2NC_6H_4(CH_2)_2\overset{+}{N}Me_3$	-0.42
m-$H_2NC_6H_4(CH_2)_2\overset{+}{N}Me_3$	+0.26
o-$H_2NC_6H_4(CH_2)_2\overset{+}{N}Me_3$	0.56
$C_6H_5(CH_2)_3\overset{+}{N}Me_3$	0.58
m-$O_2NC_6H_4(CH_2)_2\overset{+}{N}Me_3$	0.62
m-$ClC_6H_4(CH_2)_2\overset{+}{N}Me_3$	0.70
p-$HOC_6H_4(CH_2)_2\overset{+}{N}Me_3$	0.75
o-$ClC_6H_4(CH_2)_3\overset{+}{N}Me_3$	1.01
$C_6H_5(CH_2)_2\overset{+}{N}Me_3$	1.05
m-$BrC_6H_4CH_2\overset{+}{N}Me_3$	1.12
p-$HOC_6H_4(CH_2)_3\overset{+}{N}Me_3$	1.30

The most active agonists are shown in table 14. Hydroxy and amino substituted compounds are very active, but chloro compounds are not as potent, especially considering their high affinity in the antagonist series. In general high affinity does not seem associated with high activity. One example of this was the low affinity of the benzyldiethylamino compounds which were partial agonists.

There does not appear to be any correlation with the theories of Hey (1952) or Sekul & Holland (1961). The influence of the substituents in this type of compound seems to involve several factors which may act in opposite directions. However, it may be that if more sophisticated information about the molecules was available, a correlation between structure and activity might be observed.

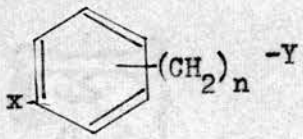
Electron charge distributions and interatomic distances of preferred conformations of the molecules would be available from molecular orbital calculations and measurement of n. m. r. spectra, and this information may shed light on the problem.

The use of the compounds which have been prepared is limited because they are mainly quaternary salts and would not be suitable as a substitute for nicotine in tobacco. The action of p-hydroxybenzyldiethylamine as a tertiary curare-like compound may make it suitable as a substitute for dihydro-β-erythroidine.

SYNTHETIC CHEMISTRY

Chemistry

Introduction. It was originally intended to make the following series of compounds.



where x = NO_2, Cl, Br, OMe, OH, NH_2.

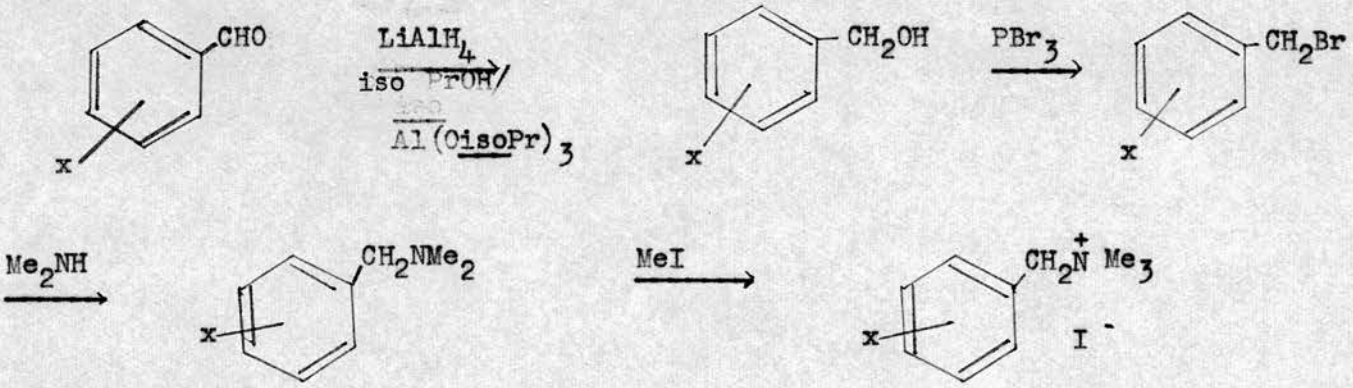
Y = - $\overset{+}{N}Me_3$ and $\overset{+}{N}Et_3$

n = 1, 2, 3.

It was not found possible to make all of them, particularly the ortho substituted benzyltriethylammonium salts. In these series the hydrobromide of the corresponding tertiary base was made. To compare affinity constants of these tertiary bases with the quaternary salts many other tertiary hydrobromides were prepared.

Of the compounds where n= 3, only the series in which x = Cl, O Me, OH were made.

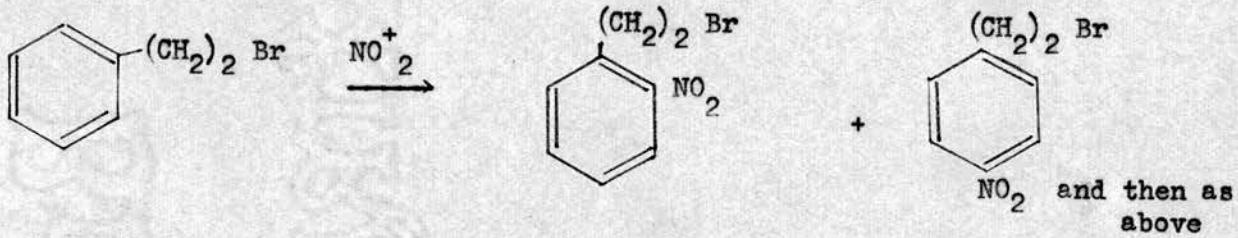
The general method for synthesis of the benzyl compounds was as follows.



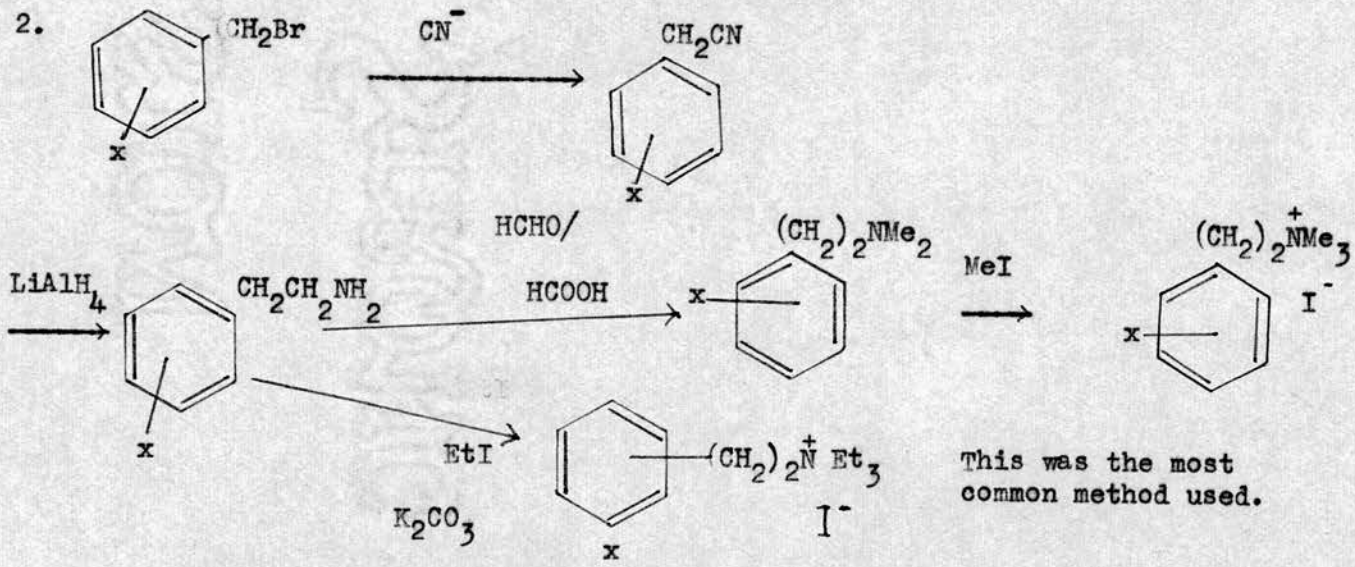
By using diethylamine and ethyl iodide, the triethylammonium components could similarly be synthesised.

The phenethyl compounds were prepared by one of the following routes.

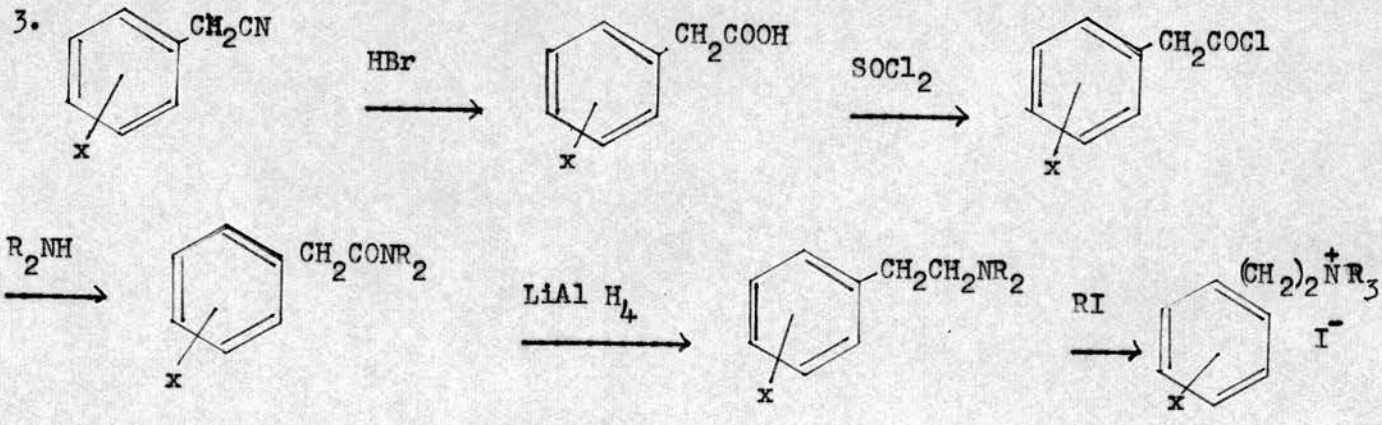
1. o and p nitro compounds were prepared as follows.



2.

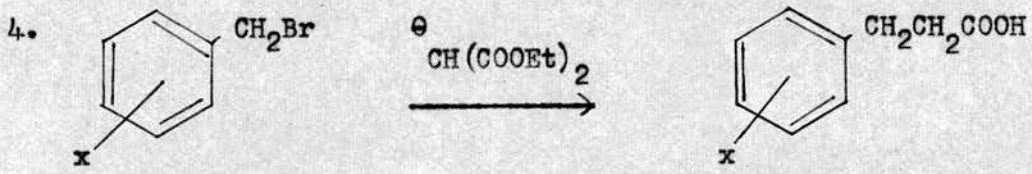


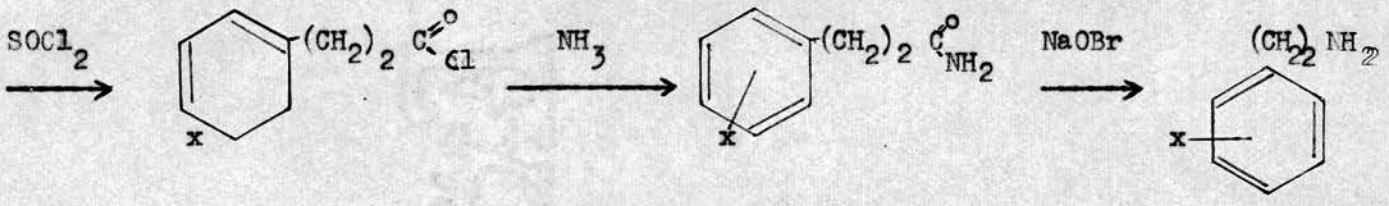
3.



where R = Me or Et.

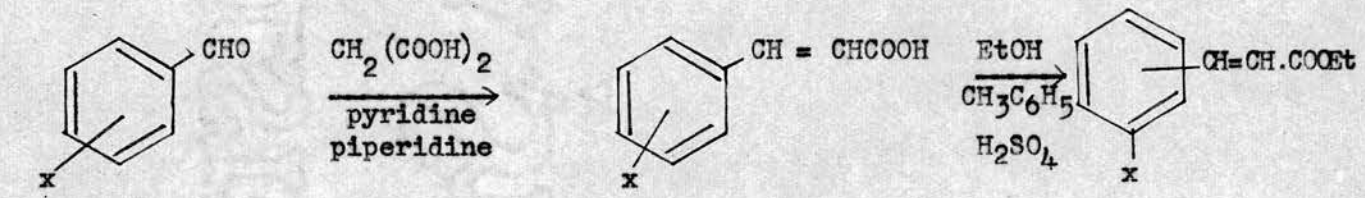
4.

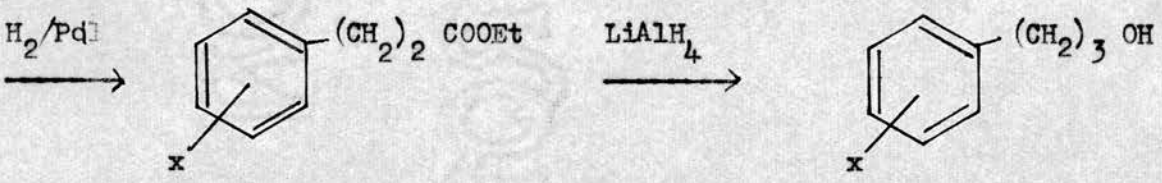




This was continued as in 2.

The phenylpropyl compounds were prepared as follows.





The quaternary salt was prepared via the bromide and tertiary base.

Table I MeO C_6H_4 CHO

	Yield	b.p.	n_D^{25}
o	84%	128-32°/10 mm. 243-4°/754 mm.[2]	1.5435
m	85%	62-7°/0.2 mm. 88-90°/3 mm.[1]	1.5518
p	82%	116-20°/10 mm. 248°/760 mm.[3]	1.5718

1. Ieke (1949)
2. Posner (1910)
3. Tiemann & Herzfeld (1877)

Experimental

In all tables, properties on the upper line are observed, those on the lower line are literature.

Melting points were determined using either a Koffler hot stage microscope or a Mettler FPI automatic melting point apparatus.

Analyses for ionic halogen were determined gravimetrically. An excess of silver nitrate solution containing 2% nitric acid was added to 50-150 mg of sample, and the precipitated silver halide was subsequently weighed.

(i) Benzyl compounds (n = 1)

Usually the substituted benzaldehyde was the starting material, although sometimes the benzyl alcohol or bromide was commercially available.

The methoxy benzaldehydes were prepared by methylation of the corresponding hydroxy benzaldehyde using dimethyl sulphate and dilute sodium hydroxide exactly as described by Icke et.al. (1949). Yields and properties are summarised in table I.

Benzyl alcohols. In all reductions with lithium aluminium hydride the methods used were those described by Brown (1951). For the preparation of alcohol from aldehyde the following description is typical.

m-chlorobenzaldehyde (13.6g; 0.1 mole) dissolved in ether (100 mls) was added dropwise to lithium aluminium hydride (2g; 0.05 mole) in ether (200 mls) in a 1 litre flask fitted with a reflux condenser. The rate of addition was adjusted so as to keep the ether gently boiling. The mixture was then heated under reflux for two hours. An excess of water was carefully added, followed

Table 2 $X.C_6H_4-CH_2OH$

X	Yield	b.p.	m.p.	n_D^{25}
o - Cl	89%		68-70° (aqueous EtOH) 64-5° C [1.]	
p - Cl	85%	126-32°/10 mm	71-3° 71-72.5°C [1.]	
o - OMe	81%	112-8°/10 mm 120-122°/10 mm [2]		1.5398
m - OMe	82%	125°/12 mm [3]		1.5432

1. Carothers & Adams (1924)
2. Iddles, French, Mellon (1932)
3. Rapson, Robinson (1935)

Table 3 $X.C_6H_4.CH_2Br$

X	b.p.	m.p.	Yield
o - Cl	98°/10 mm. 102°/ 9 mm.		86%
p - Cl		48-50° (EtOH) 51° 1.	94%
o - NO_2		46-47.5° (EtOH) 46-7° 2.	65%
m - NO_2		56-8° (EtOH) 58-9° 2.	90%
o - OMe	115-8°/10 mm. 112°/12 mm. 4		78%
m - OMe	117-22°/10 mm. 123-5°/13 mm. 3		92%
p - OMe	128°/10 mm. 104°/1.5 mm. 5		85%

1. Shoesmith Slater (1926)
2. Norris, Watt (1916)
3. Pintado (1955)
4. Baltrop (1946)
5. Baker (1932)

by dilute hydrochloric acid (200 mls of 50%). The mixture was extracted several times with ether, the extract washed with water, dried with magnesium sulphate, filtered, and the ether distilled off. Fractionation of the residue gave 12.5 g (92%) of product b.p. = 124-5°/10mm; n_D^{25} = 1.5544 Mettler (1905) gives b.p. = 234°. Yields and properties of other benzyl alcohols are shown in table 2.

The Meerwin-Pondoff-Varley method was used for the reduction of nitrobenzaldehydes because lithium aluminium hydride reduces them to azo compounds. The method used was that described by Wilds (1944).

m-nitrobenzyl alcohol was obtained in 86% yield; b.p. = 112-122°/0.05mm; n_D^{25} = 1.5734. Thorp and Wildman (1914) gave b.p. = 175-80°/3mm

o-nitrobenzyl alcohol was obtained in 95% yield; m.p. = 73-4° from water. Pierron (1901) gives m.p. = 74°.

Benzyl Bromides. These were obtained from the corresponding benzyl alcohol and phosphorus tribromide. The prep. of chlorobenzyl bromide is typical.

Phosphorus tribromide (10 mls) in chloroform (50 mls) was added dropwise to m-chlorobenzyl alcohol (18.5 g, 0.13 mole). The mixture was then heated under reflux for 30 minutes and water (30 mls) carefully added. The chloroform layer was washed, dried, filtered; and distilled. Yield = 24.1g (95%); b.p. = 114-5°/10mm; n_D^{25} = 1.5825.

Shoesmith and Slater (1926) give b.p. = 109°/10mm.

Properties and yields of other benzyl bromides are shown in table 3.

Table 4a $X.C_6H_4 CH_2 NMe_2$

x	Yield	b.p.	n_D^{25}	m.p. of hydrobromide	% Br^- reqd.	% Br^- found
o-Cl	64%	86°/10mm.	1.5212	194.8-195.2° (MEK/EtOAc)	31.94	31.85
		90°/13mm.[4]				
m-Cl	37%	94-6°/10mm.	1.5186	194.7-195.2° (MEK/EtOAc)	31.94	32.10
p-Cl	54%	94-5°/10mm.	1.5176	194.1-194.4° (MEK/EtOAc)	31.94	32.20
		90-95°/10mm.[5]				
o-NO_2	92%	124°/10mm.	1.5306			
		133°/16mm.[3]				
m-NO_2	82%	140-142°/10mm.	1.5356			
		144°/16mm.[3]				
p-NO_2	83%	144-146°/10mm.	1.5394			
		146°/16mm.[3]				
o-OMe	68%	93-96°/10mm.	1.5148			
		113°/20mm.[2]				
m-OMe	75%	108°/10mm.				
		105°/13mm.				
p-OMe	82%	106°/16mm.				
		109°/13mm.[2]				
m-Br	73%	100-2°/10mm.	1.5428			
		105-8°/9.8mm.	1.5388[6]			
p-Br	91%	98-9°/10mm.	1.5413			
		121-2°/15mm.	1.5406[1]			

Table 4b $X.C_6H_4 CH_2 NEt_2$

x	Yield	b.p.	n_D^{25}	m.p. of hydrobromide	% Br^- calcd.	% Br^- found
o-Cl	89%	108°/10mm	1.5122	158.9-159.4° (MEK/EtOAc)	28.82	28.85
m-Cl	82%	116-8°/10mm	1.5115	201.7-202.6° (MEK/EtOAc)	28.82	28.82
p-Cl	91%	118-20°/10mm	1.5098	126.2-127.3° (MEK/EtOAc)	28.82	28.61
o-NO_2	97%	143-4°/10mm 144°/13mm[1].	1.5198	151.0-152.5° (MEK/EtOAc)	27.65	27.61
m-NO_2	90%	160-2°/10mm 158/13mm[1].	1.5238	184-90° (MEK/EtOAc)	27.65	27.95
p-NO_2	90%	162-6°/10mm 160°/13mm[1].	1.5284	121.3-121.9° (MEK/EtOAc)	27.65	27.51
o-OMe	89%	122-4°/10mm 113-4°/6mm[3]	1.5066	120.2-121° (MEK/EtOAc)	29.19	29.49
m-OMe	92%	126-8°/10mm 132-5°/10mm[2].		145.3-146.0° (MEK/EtOAc)	29.19	29.38
p-OMe	85%	124-6°/10mm 121-2°/6mm[3].		104.8-105.6° (MEK/EtOAc)	29.19	29.19
m-Br	86%	145-52°/10mm	1.5305			
p-Br	84%	122-3°/10mm	1.5298			

4a Refs.
1. Dewhirst & Cram (1958)
2. Stedman (1927)
3. Bennet & Willis (1929)
4. Von Braun, Kühn & Weismantel (1926)
5. Eliel, Ferdinand, Herrmann (1954)
6. Beard, Van Benan & Hauser (1961)

4b Refs.
1. Bennet & Willis (1929)
2. McCoubrey (1951)
3. Pintado (1955)

Benzyl dimethylamines and diethylamines.

These were prepared from the corresponding benzyl bromide and dimethylamine or diethylamine respectively.

The benzyl bromide (0.05 mole) was heated under reflux for six hours with dimethylamine or diethylamine (0.1 mole) in alcohol (100 mls). Most of the solvent was removed under vaccuum. A very strong solution of potassium hydroxide was added and the tertiary amine was extracted with ether, the extract washed, dried, and distilled.

Portions of most of the diethylamines were converted to their hydrobromide. The amine (about 1g) was dissolved in ethanol (50 mls) and concentrated hydrobromic acid was added until the solution was strongly acid to B.D.H. Universal indicator paper. The solvent was removed under vaccuum, more ethanol added, and the solution again evaporated under vaccuum. If the material did not crystallise spontaneously, crystallisation was induced by scraping the residue. Yields and properties of the amines, also melting points, solvents for recrystallisation, and analyses for the hydrobromides are shown in table 4a and b.

Hydroxy benzyl dimethylamines and diethylamines were prepared from the corresponding methoxy compounds by hydrolysis with concentrated hydrobromic acid.

The tertiary amine (5g) was heated under reflux overnight with concentrated hydrobromic acid (50 mls); cooled, and a solution of potassium hydroxide added until a dense cloudiness occurred. This mixture was then extracted with ether. Because the product was soluble in strong acid and

Table 5a $H_2N\,C_6H_4\,CH_2NMe_2$

Pt. of attachment	Yield	b.p.	n_D^{25}
o	66%	94-6°/10mm 107°/14mm[1].	
m	87%	127°/10mm 129°/13mm[1].	
p	90%	130-131°/10mm 133°/16mm[1]	1.5592

1. Stedman (1927)

Table 5b $H_2N\,C_6H_4\,CH_2NEt_2$

Pt. of attachment	Yield	b.p.	n_D^{25}	m.p.of dihydrobromide	%Br calcd	%Br found
o	68%	125°/10mm 152°/40mm[1].		172-80° (sub) (MEK-EtOH)	47.04	47.32
m	76%	143°/10mm	1.5420	215.7-216.6° (EtOH)	47.04	47.13
p	83%	144°/10mm 145°/12mm[1].	1.5412	186-90° (MEK-EtOH)	47.04	47.28

1. Hall & Turner (1945)

strong alkali, the pH of the mixture had to be carefully controlled. The technique used was to adjust the pH by small amounts each way until turbidity occurred and then extract with ether. When addition of acid or alkali produced no turbidity, it was assumed that the extraction was complete. The extract was dried, filtered, and the ether taken off.

o- hydroxy benzyl dimethylamine was distilled and obtained in 68% yield; b.p. = 92°/10mm; n_D^{25} = 1.5208. Stedman (1927) gave b.p. = 99-100°/12mm.

o- hydroxy benzyl diethylamine was distilled and obtained in 72% yield; b.p. = 121°/10mm.

n_D^{25} = 1.5136. Its hydrobromide had m.p. = 255-7°; % Br^- calcd. = 30.77%; found = 31.03%.

Crude p - hydroxy benzyl dimethylamine was used for the next stage.

p - hydroxy benzyl diethylamine was puridied by formation of the hydrobromide; m.p. = 151.7° - 152.3°; % Br^- calcd. = 30.77%, % Br^- found = 30.48%.

m - hydroxy benzyldimethylamine was purified by formation of the hydrobromide; m.p. = 134.4-134.5°C; % Br^- calcd. = 34.48%, % found = 34.23%.

p - hydroxy benzyldiethylamine was also obtained as the hydrobromide; % Br^- calcd. = 30.77%, % found = 30.92%.

Amino-benzyldimethylamines and diethylamines

These were prepared from the corresponding nitro compound by catalytic hydrogenation.

Nitrobenzyldialkylamine (0.025 mole) in ethanol (50 mls) was stirred vigorously with platinum-charcoal catalyst (0.2g) in an atmosphere of hydrogen at room temperature and pressure. After uptake of the theoretical amount of hydrogen the mixture was filtered and the product distilled. Yields and properties are shown in table 5a and b.

Table 6a $X.C_6H_4CH_2\overset{+}{N}Me_3\ I^-$

X	Yield	m.p. -	%I^- required	%I^- found
o-Cl	57%	161.5-162°	40.75	41.03
m-Cl	68%	199-200°	40.75	41.01
p-Cl	73%	260-261°	40.75	40.54
o-NO_2	61%	204-5°	39.43	39.14
m-NO_2	67%	206-206.5°	39.43	39.52
p-NO_2	65%	203-4° 198° 1.	39.43	39.45
o-NH_2	42%	170.2-170.4°	43.49	43.74
m-NH_2	58%	157-157.5°	43.49	43.20
p-NH_2	60%	140.0-140.2°	43.49	43.37
o-OH	53%	171.4-171.5° 169° 1.	43.34	43.38
m-OH	64%	171.1-171.8°	43.34	43.64
p-OH	71%	184-6°	43.34	43.61
o-OMe	68%	162.2-162.9°	41.36	41.47
m-OMe	79%	143.5-144.3°	41.36	41.17
p-OMe	83%	157.1-158.1°	41.36	41.65
m-Br	76%	208-211°	35.7	35.4
p-Br	79%	233-237°	35.7	35.7

1. Stedman (1927)

Table 6b X C_6H_4 CH_2 $\overset{+}{N}Et_3$ I^-

X	Yield	m.p.	%I^- required	%I^- found
m-NO_2	64%	206-207.5°	39.43	39.52
m-Cl	68%	159-60°	35.85	35.67
p-Cl	67%	193.4-194.4°	35.85	35.75
m-NH_2	54%	186-7°	H = 6.93 C = 46.91	7.02 46.73
m-OH	56%	139-40°	37.91	37.85
m-Br	65%	189-190°	31.91	31.81
p-Br	67%	186-188°	31.91	32.06

Table 7 Cl C_6H_4 CH_2 CN

Point of attachment	Yield	b.p.	n_D^{25}
m	85%	124-31°/10mm 261°/757mm [1].	1.5402
p	71%	125-134°/10mm	

1. Kenner & Morton (1934)

Quaternary ammonium salts.

The tertiary amine (0.025 mole); dissolved in butan-2-one (50 mls); was allowed to react with alkyl iodide (0.05 mole) at room temperature for two hours. The mixtures were then heated under reflux, for ten minutes - for the preparation of trimethylammonium salts, and for several hours for the preparation of triethylammonium salts. The mixture was cooled and ethyl acetate added to precipitate any dissolved quaternary salts. The products were recrystallised from butan-2-one (methyl ethyl ketone) with the addition of a small volume of ethanol.

Great difficulty was experienced in preparing the ortho substituted benzyltriethylammonium salts. After heating under reflux for twelve hours as above the tertiary base could be recovered unchanged. This was presumably due to steric interaction between the ortho substituent and the nitrogen to be quaternised.

Many of the compounds were chromatographed on paper and found to be homogeneous using a solvent system of butanol/ethanol/water (5:5:2), and developed with modified Dragendorff reagent (Thies and Reuther 1954). Yields, melting points, and analyses are given in table 6a and b.

(ii) Phenethyl Compounds (n = 2)

o and p - nitrophenethyl bromides. The nitration of phenethyl bromide (92g; 0.5 mole) with fuming nitric acid, acetic anhydride, and acetic acid was carried out as described by Foreman & McElvain (1940). The crude product was crystallised from 60-80° petrol (1½ l) and 59g (51%) of p-nitrophenethyl bromide was obtained m.p. = 62-5°. Foreman & McElvain gave 69-70°.

The residue was then distilled under reduced pressure yielding 45g product b.p. 100-110°/ 0.1mm. Foreman gave 115-20° (0.5mm). After recrystallisation 38g (33%) o - nitrophenethyl bromide was obtained. m.p. = 30-33°C. Foreman gave 36-8°C.

Prepn. of chlorobenzyl cyanides. The method used was similar to that of Adams and Thal (1922). The prepn. of o chlorobenzyl cyanide is typical.

Potassium cyanide (10.4g; 0.15 mole) was heated on a water bath with water (10 mls) until most of the potassium cyanide had dissolved. o-chlorobenzyl bromide (26.0g; 0.13 mole) in ethanol (25 mls) were slowly added and the mixture heated under reflux for 4 hours. Most of the alcohol was distilled off and an excess of water added. The mixture was extracted with ether, the extract washed with water, dried, and distilled. 15.1g (80%) o-chlorobenzyl cyanide were obtained b.p. = 112-6°/10mm; n_D^{25} = 1.5435.

Yields and properties of other chlorobenzyl cyanides are shown in table 7.

Prepn. of methoxybenzyl cyanides. The method used was that of Rorig (1956) who treated p-methoxybenzyl alcohol with concentrated hydrochloric acid and

Table 8 MeO C_6H_4 CH_2 CN

Point of attachment	Yield	b.p.	n_D^{25}
o	61%	137-42°/10mm	
m	53%	139-46°/10mm	1.5269
p	51%	105-10°/0.2mm	1.5310
		94-97°/0.3mm	1.5291 [1.]

1. Rorig (1956)

Table 9 X C_6H_4 $CH_2CH_2NH_2$

X	Yield	b.p.	n_D^{25}
o-Cl	57%	166-110°/10mm	1.5491
m-Cl	54%	111-121°/10mm	1.5442
p-Cl	56%	118-120°/10mm	1.5443
o-OMe	46%	119-26°/10mm	
m-OMe	49%	125-132°/10mm	1.5314
p-OMe	45%	77-79°/0.15mm	1.5357
		136-8°/18mm [1.]	

1. Rosenmund (1909)

reacted the crude product with sodium cyanide, sodium iodide, and dry acetone. For the preparation of o and m-methoxybenzylchlorides the reaction had to be modified. The mixture of hydrochloric acid and methoxybenzyl alcohol was warmed on a water bath to about 60° and stirred vigorously for one hour. The mixture was then cooled and extracted with ether, the extract dried, and the ether distilled off. If an infra-red spectrum of the residue did not show a hydroxyl peak, the reaction was taken to be complete. Otherwise the procedure was repeated with fresh hydrochloric acid. The reaction sometimes took as long as five hours.

Yields and properties of methoxybenzyl cyanides are shown in table 8.

Chloro and methoxy phenethylamines. The corresponding substituted benzyl cyanides were reduced with lithium aluminium hydride as described by Amundsen & Nelson (1951). Properties and yields are shown in table 9.

m-nitrophenyl propionic acid

m-nitrobenzyl bromide (43g; 0.2 mole) in ethanol (300 mls) was added to a solution of sodiomalonic ester; prepared from ethyl malonate (64g; 0.4 mole); sodium (92g, 0.4 mole) and ethanol (200 mls). The mixture was boiled under reflux for four hours and most of the alcohol removed by distillation. An excess of concentrated hydrogen bromide solution was added to the mixture, which was then heated under reflux for about twenty hours. During this time the ethyl bromide, which was formed in the reaction, was distilled off to prevent the temperature from being lowered. The mixture was cooled, water added, and the organic layer extracted with benzene. The extract was washed,

dried,and the ether removed by distillation. After recrystallisation from water 18.0g (47%) m-nitrophenyl propionic acid was obtained. m.p. = 113-7°C. Gulland & Haworth (1929) gave 117-8°C.

The low yield was disappointing and the reaction was repeated using alcohol which had been dried by distillation from magnesium methoxide. However, a similar yield to above was obtained.

m-nitrophenyl propionamide. (Gulland and Haworth (1929)

m-nitrophenyl propionic acid (12g, 0.06 mole) and thionyl chloride (12 mls) were heated under reflux for two hours. The remaining thionyl chloride was removed by distillation and the residue poured carefully into concentrated ammonia solution. The precipitated amide was collected and recrystallised from benzene. This yielded 10g. (84%) m-nitrophenyl propionamide m.p. = 96-98°C. Gulland and Haworth gave 99°C.

m-nitrophenethylamine

A solution of sodium hypobromite was prepared by adding bromine (1.2 mls) to a solution of sodium hydroxide (4.8 g) in water (40mls) at 0°C.

To the cold solution was added m-nitrophenyl propionamide (3.9g, 0.2 mole) and the mixture was shaken until the solid had dissolved.

The solution was heated to 60° on a water bath, cooled, and extracted with benzene. The extract was washed, dried, and distilled.

2.1g (63%) of product were obtained b.p. = 154°/10 mm. n_D^{25} = 1.5682.

Table 10a X C_6H_4 $(CH_2)_2N$ Me_2

X	Yield	b.p.	n_D^{25}
o-NO_2	64%	146-156°/10mm 126-130°/1mm [1.]	1.5336
p-NO_2	81%	150-153°/10mm 142-4°/1mm [1.]	1.5402
o-Br	58%	112°/10mm	1.5408
m-Br	86%	116-121°/10mm	1.5418
p-Br	63%	123-126°/16mm	1.5408

1. Dale and Buell (1956)

Table 10b X C_6H_4 $(CH_2)_2$ NEt_2

x	Yield	b.p.	n_D^{25}
o-NO_2	53%	160-162°/10mm 120-3°/1mm	1.5262
p-NO_2	63%	166-168°/16mm 143-8°/1mm [1.]	1.5298
o-Br	56%	138°/10mm	1.5330
m-Br	78%	132-40°/10mm	1.5327
p-Br	66%	142-4°/10mm	1.5310

1. Dale and Buell (1956)

Substituted phenethyl dimethylamines and diethylamines.

The amines shown in table 10 a and b were prepared from the corresponding phenethyl bromides by reaction with dimethylamine and diethylamine exactly as described for the benzyl compounds.

o and p-aminophenethyl dimethylamines and diethylamines.

The corresponding nitrophenethylamine was reduced using platinum catalyst as described for the benzyl compounds. Yields and properties are shown in table 11.

m-aminophenethyl trimethylammonium and triethylammonium iodides were prepared by the general method (3) starting with m-nitrobenzyl bromide, which was converted to the cyanide in 68% yield by the method already described. b.p. of cyanide = 144-8°/10mm; m.p. = 57-9°C.

m-nitrophenyl acetic acid Robertson (1922)

m-nitrobenzyl cyanide (12.0g, 0.075 mole); water (35 mls); sulphuric acid (38 mls) were boiled under reflux for fifteen minutes, diluted with an equal volume of water, cooled to 0°C, and the precipitate was collected. After recrystallisation from water, this yielded 11.1g (83%) product. m.p. = 118-9°C.

m-nitrophenylacetyl chloride

m-nitrophenyl acetic acid (4.5g, 0.025 mole) was boiled under reflux for 30 minutes with an excess of thionyl chloride. The thionyl chloride was removed by distillation under reduced pressure and the residue fractionated. This yielded 4.0g (82%) product. b.p. = 126-9°/0.15 mm; m.p. = 64-9°C.

N, N-dimethyl and N, N-diethyl, m-nitrophenyl acetamide

To a solution of anhydrous dimethylamine in ether (40 mls, 20%), in a 250 ml. flask fitted with a cold trap containing solid carbon dioxide and acetone, was added m-nitrophenylacetyl chloride (4g 0.02 mole) in ether (25 mls). The precipitated dimethylamine hydrochloride was filtered and the filtrate distilled under reduced pressure. 3.6 g (94%) of product was obtained b.p. = 162-167°/0.1mm. b.p. = 47-49°.

The diethylamide was prepared similarly (in 94% yield) using diethylamine. b.p. = 165-168°C/0.03mm; n_D^{25} = 1.5448.

m-aminophenylacet - N, N dimethyl and -N, N-diethylamide.

The corresponding nitro amides were reduced catalytically in a similar way to that already described except that Raney nickel catalyst was used. Both platinum charcoal and palladium charcoal were found to be ineffective, possibly because they are more readily poisoned than nickel.

Dimethylamide was obtained in 60% yield; b.p. = 165-6°/0.15mm, m.p. = 82-3°.

Diethylamide was obtained in 79% yield; b.p. = 163-8°/0.1 mm.

m-aminophenethyldimethylamine and diethylamine.

The amides were reduced with lithium aluminium hydride using a modification of the method already described.

m-aminophenylacet-(N, N di methyl)-amide (2.1 g, 0.013 mole) was placed in the thimble of a Soxhlet extractor. The extractor was fitted with a reflux condenser and mounted in a 500 ml. flask containing lithium aluminium

Table 11 $H_2N\ C_6H_4\ (CH_2)_2\ X$

Pt. of attachment	X	Yield	b.p.	n_D^{25}
o	NMe_2	74%	123-132°/10mm	1.5480
p	NMe_2	76%	138-140°/10mm	1.5489
o	NEt_2	64%	140-142°/10mm	1.5394
p	NEt_2	79%	146-148°/10mm	1.5374

Table 12 $X - C_6H_4\ (CH_2)_2\ NMe_2$

x	Yield	b.p.	n_D^{25}
o-Cl	98%	98-104°/10mm	1.5200
m-Cl	83%	105-114°/10mm	1.5195
p-Cl	78%	106-18°/10mm	1.5188
o-OMe	83%	131-4°/10mm	1.5120
m-OMe	81%	136-142°/10mm	1.5352
p-OMe	83%	127-131°/10mm	1.5098

hydride (0.52g, 0.013 mole) in ether (150 mls). The ether was boiled by means of a heating mantle until all the amide in the extractor had dissolved. The mixture was cooled and sufficient water added to decompose the excess lithium aluminium hydride. This was followed by sodium hydroxide solution (150 mls, 10%). The ether layer was separated and the aqueous layer extracted twice more with ether. The combined extract was washed, dried, and fractionated.

m-aminophenethyldimethylamine (1.3g, 68%) was obtained.

b.p. = 144-9°C/10mm, m.p. = 33.8°C.

m-aminophenethyldiethylamine was similarly prepared in 80% yield.

b.p. = 155-7°/10 mm, n_D^{25} = 1.5386.

Substituted phenethyl dimethylamines

These were prepared from corresponding phenethylamines by the Eschweiler-Clarke procedure (Moore 1949). m-nitrophenethyldimethylamine serves as an example.

m-nitrophenethylamine (2.0g, 0.012 mole), formic acid (2.5g, 0.054 mole), and formaldehyde solution (3.6 mls, 37%) were heated on a water bath for 4 hours. The mixture was cooled, strong potassium hydroxide solution added, and the organic layer extracted with ether. The extract was washed, dried and distilled at reduced pressure.

1.9g (81%) m-nitrophenethyldimethylamine was obtained. b.p. = 147-9°/10 mm n_D^{25} = 1.5336.

Yields and properties of other phenethyldimethylamines are shown in table 12.

Hydroxyphenethyl dimethylamines

Portions of the corresponding methoxy compounds were treated with hydrobromic acid in an analagous way to the benzyl series. Due to the small quantity involved, the crude products were used for the quaternisation.

m-hydroxyphenethyldimethylamine was prepared by another route as well as the above way.

m-methoxy cinnamic acid. This was prepared by the Doebner modification of the Perkin reaction (Johnson (1942)

m-methoxybenzaldehyde (45g, 0.3 mole), malonic acid (60g, 0.576 mole) dry pyridine (120 mls) and piperidine (3 mls) in a 500 mls. flask, fitted with a reflux condenser and drying tube, were heated for two hours on a water bath. The solution was cooled and poured into a mixture of concentrated hydrochloric acid (175 mls) and ice (300 g). The precipitate was filtered and washed with dilute hydrochloric acid and water. After drying and recrystallisation from water/ethanol, 52g (88%) m-methoxybenzaldehyde were obtained m.p. 113-6°C.

m-methoxyphenylpropionic acid

m-methoxycinnamic acid (26g, 0.146 mole) in alcohol (150 mls) was reduced using palladium charcoal catalyst and hydrogen. 23.4g (90%) product was obtained m.p. = 43°C.

Table 13a $XC_6H_4(CH_2)_2\overset{+}{N}Me_3I^-$

	Solvent for recrystallisation	m.p.	%I^- calcd.	%I^- found	Yield
o-Cl	EtOH/MeOH	258-261°	39.01	39.06	67%
m-Cl	MEK/EtOH	209-210°	39.01	39.03	76%
		206-8° [1]			
p-Cl	MEK/EtOH	250-253°	39.01	39.28	78%
o-NO_2	MEK/EtOH	242-245°	37.80	38.00	71%
m-NO_2	MEK/EtOH	245-6°	37.80	38.08	82%
p-NO_2	MEK/EtOH	212-4°	37.80	37.77	74%
o-NH_2	MEK/EtOH	218-220°	41.51	41.81	58%
m-NH_2	MEK/EtOH	204-6°	41.51	41.36	64%
p-NH_2	MEK/EtOH	220-221°	41.51	41.48	62%
o-OMe	MEK/EtOH	211.3-211.7°	39.57	39.52	56%
m-OMe	MEK/EtOH	182.3-182.6°	39.57	39.64	78%
		186-8° [1]			
p-OMe	MEK/EtOH	211.4-211.7°	39.57	39.86	83%
o-OH	MEK/EtOH	226.2-226.5°	41.37	41.23	62%
m-OH	MeOH	244.3-245.0°	41.37	41.40	68%
p-OH	MEK/EtOH	227.4-227.7°	41.37	41.62	69%
o-Br	MEK/EtOH	181.2-181.3°C	34.51	34.41	58%
m-Br	MEK/EtOH	136.5-137.4°C	34.51	34.22	67%
p-Br	MEK/EtOH	195.1-195.2°	34.51	34.20	73%

1. Glässer and Pasini (1960)

m-methoxyphenethylamine

m-methoxyphenylpropionic acid (23.4g) was converted to the amide in the same way as m-nitrophenylpropionic acid. Distillation gave 15.5 g. (67%) m-methoxyphenylpropionamide. b.p. = 159-60°/0.04 mm. m.p. = 56°.

5.4 g of this was converted by the Hoffman reaction into m-methoxyphenethylamine as for the m-nitro analogue. Fractionation yielded 2.9g (63%) product. b.p. = 124-7°/10 mm. n_D^{25} = 1.5372.

m-Hydroxyphenethyldimethylamine

m-methoxyphenethylamine (2.9g) was methylated using formic acid and formaldehyde. m-methoxyphenethyldimethylamine (2.1g, 61%) was prepared b.p. = 129-136°/10mm. n_D^{25} = 1.5290.

The ether group was hydrolysed with concentrated hydrobromic acid to yield 1.9 g (71%). m-hydroxyphenethyldimethylamine. m.p. = 174°.

Quaternary ammonium salts

Tertiary amines were quaternised exactly as described for the benzyl compounds. Yields and properties are shown in table 13 (a) and (b).

Unfortunately, the bromo triethylammonium compounds were not prepared. Long periods of refluxing of the tertiary bases with ethyl iodide did not produce any product.

Phenethyl triethylammonium salts.

When the primary rather than the tertiary amine was available the following method was used to prepare the triethylammonium iodides.

Table 13b $X.C_6H_4(CH_2)_2\overset{+}{N}Et_3\ I^-$

X	Yield	Solvent for recrystallisation	m.p.	%I^- calcd.	%I^- found
o-NO_2	64%	MEK/EtOH	167-172°	33.59	33.61
p-NO_2	68%	MEK/EtOH	168-70°	33.59	33.88
o-NH_2	62%	MEK/EtOH	204.6-204.8°	36.50	36.68
p-NH_2	73%	MEK/EtOH	224.9-225.2°	36.50	36.07
m-NH_2	68%	MEK/EtOH	152-153°C	36.50	36.35

Table 14 $X.C_6H_4(CH_2)_2\overset{+}{N}Et_3\ I^-$

X	Yield	Solvent for recrystallisation	m.p.	%I^- calcd.	%I^- found
o-Cl	68%	MEK/EtOH	185-6°	34.55	34.84
m-Cl	78%	MEK/EtOH	108-108.5°	34.55	34.52
p-Cl	81%	MEK/EtOH	250-251°	34.55	34.78
o-OMe	72%	MEK/EtOH	159.6-160.3°	34.98	35.12
m-OMe	82%	MEK/EtOH	103.7-104.2°	34.98	34.82
p-OMe	80%	EtOH	164.9-165.3°	34.98	34.85
m-NO_2 (Br^-)	65%	MEK/EtOH	211-212°	24.17 (Br^-)	24.05

Substituted phenethylamine (0.018 mole), potassium carbonate (3.8 g, 0.028 mole) and ethyl iodide (10 mls) in acetone (45 mls) and water (5 mls) were heated under reflux on a water bath for four hours. The mixture was then filtered hot and the solvent removed. The residue was the desired quaternary salt contaminated with inorganic salts - mainly potassium iodide. After thorough drying the crude product was dissolved in butan-2-one/ethanol mixture and filtered hot. This removed the inorganic material, and on cooling, the quaternary iodide was precipitated.

m-nitrophenethyltriethylammonium iodide could not be obtained pure enough. It was dissolved in the minimum of water and passed down a column of anion exchange resin (I.R.A. 400). The column was washed with water until the eluted liquid was neutral to litmus. The pooled washings were neutralised with hydrobromic acid and evaporated to dryness. The product was then recrystallised in the usual way.

Quaternaries made this way are shown in table 14.

Hydroxyphenethyltriethylammonium iodides.

These were made by hydrolysis of the corresponding methoxy compounds with hydriodic acid in the way described by Glässer & Pasini (1960).

Methoxyphenethyltriethylammonium iodide (2g) and concentrated hydriodic acid (15 mls) were boiled under reflux for 45 minutes. Water was then removed under vaccuum, 25 mls. alcohol added, and the mixture again evaporated to dryness. A dark-coloured, semi-solid residue remained which was heated to about 70° with 40 mls water. The aqueous solution was decanted

Table 15 $HOC_6H_4(CH_2)_2\overset{+}{N}Et_3\ I^-$

Pt. of attachment	Yield	Solvent for recrystallisation	m.p.	%I^- calcd.	%I^- fou
o	55%	MEK/EtOH	181.6-182.2°	36.39	36.54
m	63%	MEK/EtOH	167.7-168.3°	36.39	36.39
p	59%	MEK/EtOH	214.7-215.0°	36.39	36.30

Table 16 $Cl.C_6H_4(CH_2)_2X\ .\ HBr$

Pt. of attachment	X	m.p.	%Br^- calcd.	%Br^- Found
o	NMe_2	139.8-140.6°	30.25	30.38
m	NMe_2	146.4-147.2°	30.25	30.42
o	NEt_2	129.2-129.8°	27.35	27.38
m	NEt_2	152.0-154.2°	27.35	28.22

off the residual tar and evaporated to dryness. The hydroxyphenethyltriethylammonium iodide was then recrystallised (Table 15).

In order to measure their pKa, hydrobromides of o and m chloro substituted phenethyldialkylamines were prepared. Diethylamines were prepared from the primary amine by the same method as for the quaternaries except that exactly the theoretical amount of potassium carbonate and ethyl iodide was used. m.p.'s and analyses are shown in table 16.

Table 17 $X.C_6H_4CH = CH.COOEt$

X	Yield	b.p.	n_D^{25}
o-Cl	79%	112°/10mm	1.5647
m-Cl	65%	163-6°/10mm	1.5671
p-Cl	69%	150-6°/10mm	
o-OMe	85%	176-180°/10mm	1.5705
m-OMe	70%	164-170°/10mm	1.5362
p-OMe	62%	169-175°/10mm	

Table 18 $X.C_6H_4(CH_2)_2COOEt$

X	Yield	b.p.	n_D^{25}
o-Cl	91%	80-85°/10mm	1.5094
m-Cl	87%	133-138°/10mm	1.5085
p-Cl	75%	132-139°/10mm	1.5085
o-OMe	97%	149-153°/10mm	1.5030
m-OMe	93%	152-154°/10mm	1.5022
p-OMe	92%	150-153°/10mm	1.5024
		152-3°/12mm [1]	

1. Amagat & Ramart-Lucas (1932)

Table 19 $X.C_6H_4(CH_2)_3OH$

X	Yield	b.p.	n_D^{25}
o-Cl	83%	126-133°/10mm	1.5394
m-Cl	85%	134-136°/10mm	1.5365
p-Cl	72%	143-152°/20mm	1.5402
o-OMe	76%	138-148°/10mm	1.5319
m-OMe	94%	152-158°/10mm	1.5316
p-OMe	92%	157-161°/10mm	1.5302
		162°/15mm [1].	

1. Amagat & Ramart-Lucas (1932).

Table 20 $X.C_6H_4(CH_2)_3Br$

X	Yield	b.p.	n_D^{25}
o-Cl	86%	124-131°/10mm	1.5582
p-Cl	80%	135°/10mm	1.5580
o-OMe	59%	133-138°/10mm	1.5470
m-OMe	63%	164-170°/10mm	1.5794
p-OMe	57%	142-148°/10mm	1.5463

(iii) Phenylpropyl Compounds. (n = 3)

Cinnamic acids were prepared exactly as already described for m-methoxy cinnamic acid.

The products were dried and used crude for the next stage.

Ethyl cinnamates

Cinnamic acids were esterified by the method described by Micovic (1943). After the azeotropic distillation, however, most of the remaining ethanol/toluene mixture was distilled off under reduced pressure, and sodium bicarbonate solution added to the residue to remove the sulphuric acid. The organic layer was extracted with ether, the extract washed, dried, and distilled.

Yields (based on the benzaldehyde) and properties are shown in table 17.

Ethylphenylpropionate

Ethyl cinnamates in alcohol were hydrogenated at room temperature and pressure using palladium charcoal catalyst. Uptake of hydrogen was very rapid and stopped abruptly when the theoretical amount had been absorbed. The mixture was filtered and distilled. Table 18 shows yields and properties of ethylphenylpropionate.

Phenylpropyl bromides.

Substituted ethylphenylpropionates were reduced to the corresponding phenylpropanol using lithium aluminium hydride in the usual way. (Table 19). The phenylpropanols were brominated using phosphorus tribromide for the

Table 21 $X.C_6H_4(CH_2)_3Y$

X	Y	Yield	b.p.	n_D^{25}	m.p. of Hydrobromide	%I⁻ calcd.	%I⁻ found
o-Cl	NMe_2	72%	112°/10mm	1.5408	144.4-145.2°C	28.73	28.92
m-Cl	NMe_2	78%	127-8°/10mm		127.6-128.7°	28.73	28.67
p-Cl	NMe_2	74%	131-2°/10mm		130.8-133.0°	28.73	28.83
o-Cl	NEt_2	85%	138°/10mm	1.5330	122.0-122.6°C	26.10	26.29
m-Cl	NEt_2	87%	160°/16mm		165.4-166.3°C	26.10	26.16
p-Cl	NEt_2	92%	145°/10mm		102.9-103.9°C	26.10	26.17
o-OMe	NMe_2	77%	122-5°/10mm				
m-OMe	NMe_2	74%	136-138°/10mm	1.5098			
p-OMe	NMe_2	91%	136-138°/10mm	1.5053			
o-OMe	NEt_2	90%	140-145°/10mm	1.5040			
m-OMe	NEt_2	90%	150-158°/10mm	1.5052			
p-OMe	NEt_2	74%	150-153°/10mm	1.5008			

Table 22a $X.C_6H_4(CH_2)_3\overset{+}{N}Me_3\ Y^-$

X	Y	Solvent for recrystallisation	Yield	m.p.	%halogen calcd.	%halogen f
o-Cl	Br^-	MEK/EtOH	72%	137.0-137.7°	27.35	27.17
m-Cl	Br^-	MEK	76%	102.1-102.8°	27.4	27.7
p-Cl	Br^-	MEK/EtOH	79%	154.4-154.9°	27.35	27.57
o-OMe	I^-	MEK/EtOH	64%	138.0-138.3°	37.91	37.75
m-OMe	I^-	MEK/EtOAc	81%	87.4-87.8°	37.91	37.84
p-OMe	I^-	MEK	78%	125.1-125.4°	37.91	37.73
o-OH	I^-	MEK/EtOH	62%	174.0-175.2°	39.57	39.16
m-OH	I^-	MEK/EtOH	67%	156.0-156.9°	39.57	39.57
p-OH	I^-	MEK	66%	208.3-208.7°	39.57	39.61

Table 22b $X.C_6H_4(CH_2)_3\overset{+}{N}Et_3\ Y^-$

X	Y	Solvent for recrystallisation	Yield	m.p.	%halogen calcd.	%halogen fo
o-Cl	Br^-	MEK/EtOH	69%	175.6-175.9°	23.92	24.18
m-Cl	Br^-	MEK/EtOH	74%	134.2-134.9°	23.92	23.82
p-Cl	Br^-	MEK/EtOH	73%	146.3-147.1°	23.92	23.95
o-OMe	I^-	MEK/EtOH	73%	119.8-120.5°	33.69	32.83
m-OMe	I^-	MEK/EtOAc	75%	95.0-96.0°	33.69	33.57
p-OMe	I^-	MEK	76%	101.3-101.7°	33.69	33.69
o-OH	I^-	MEK/EtOH	59%	140.9-141.4°	34.98	34.85
m-OH	I^-	MEK/EtOH	65%	141.7-142.1°	34.98	35.28
p-OH	I^-	MEK/EtOH	68%	166.2-166.4°	34.98	25.03

methoxy compounds and for all the others hydrobromic acid and sulphuric acid. The preparation of m-chlorophenylpropyl bromide serves as an example.

m-chlorophenylpropanol (20.1g, 0.12 mole), sulphuric acid (25 mls), and hydrobromic acid (75 mls) were boiled under reflux for four hours. The solution was cooled and poured into water (200 mls). The mixture was extracted with benzene, the extract washed with water, dried, and distilled. This gave 19.1g (70%) m-chlorophenylpropyl bromide, b.p. = 129-138°/10mm: n_D^{25} = 1.5580.

Other phenylpropylbromides are shown in table 20.

Phenylpropyldialkylamines were prepared in exactly the same way as for the benzyl compounds. Yields and properties are shown in table 21. Hydrobromidess of the chloro substituted compounds were also made.

Portions of methoxyphenylpropyldialkylamines were hydrolysed to the corresponding hydroxy compounds with hydrobromic acid in the same way as the benzyl homologues. The crude tertiary amines were used for the quaternisations.

The methoxy and hydroxy quaternary salts were prepared as already described from the tertiary bases but the chloro compounds were made from the phenylpropyl bromides by heating under reflux with an excess of trimethylamine or triethylamine in alcohol for four hours. Removal of alcohol and residual tertiary amine yielded the crude quaternary salt which was recrystallised in the usual way.

Properties of quaternary salts are summarised in tables 22a and b.

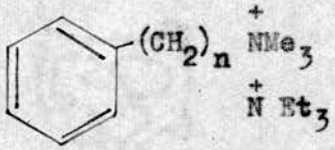
Table 23 $Ph(CH_2)_n Y$

n	Y	m.p.	%Br^- calcd.	%Br^- found
1	$\overset{+}{N}Me_3$	238-9°	19.1*	19.2
2	$\overset{+}{N}Me_3$	242-3°	32.8	32.5
3	$\overset{+}{N}Me_3$	151-2°	30.9	30.9
4	$\overset{+}{N}Me_3$	184-5°	29.4	29.3
5	$\overset{+}{N}Me_3$	168-9°	27.9	27.9
6	$\overset{+}{N}Me_3$	182.6-183.0°	26.69	26.50
7	$\overset{+}{N}Me_3$	173.3-173.5°	25.48	25.36
1	$\overset{+}{N}Et_3$	196.1-196.6°	29.41	29.37
2	$\overset{+}{N}Et_3$	134.8-135.3°	27.97	28.67
3	$\overset{+}{N}Et_3$	99.4-101.1°	26.67	26.71
4	$\overset{+}{N}Et_3$	85.8-86.6°	25.48	25.50
5	$\overset{+}{N}Et_3$		24.39	24.24
6	$\overset{+}{N}Et_3$	69.7-70.2°	23.40	23.15
7	$\overset{+}{N}Et_3$	66.6-68.5°	21.97	22.21

* chloride

Unsubstituted Compounds

The following unsubstituted phenyl compounds were obtained by standard chain lengthening procedures.



where n = 1 to 7

Starting materials were benzyl bromide and phenethyl bromide and the chains were lengthened in the following way.

e.g. $Ph\ (CH_2)_2\ Br \xrightarrow[2.\ H\ Br]{1.\ {}^{-}CH(COOEt)_2} Ph\ (CH_2)_3\ COO\ H \xrightarrow[C_6H_5CH_3,\ H_2SO_4]{EtOH} Ph\ (CH_2)_3\ COOEt$

$$\xrightarrow{LiAlH_4} Ph\ (CH_2)_4\ OH \xrightarrow{PBr_3} Ph\ (CH_2)_4\ Br \xrightarrow{Me_2NH} Ph\ (CH_2)_4 NMe_2$$

These reactions have already been described.

Trimethylammonium salts where n = 1 to 5 were prepared by Dr.Barlow.

Analyses and melting points are shown in table 23.

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Appendix I

pKa values of substituted anilines (Braude and Nachod, Ch 14)

Substituent groups	ortho	meta	para
- H	4.62	4.62	4.62
- NO_2	-0.28	2.45	0.98
- Cl	2.62	3.32	3.81
- Br	2.60	3.51	3.91
- OCH_3	4.49	4.20	5.29
- OH	4.72	4.17	5.50
- NH_2	4.47	4.88	6.08

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